Formal Total Synthesis of (±)-Merrilactone A and Studies Towards Anislactones A/B

Ph.D Thesis

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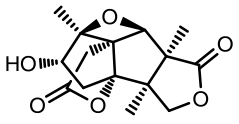
Declaration

This thesis was submitted in part fulfilment of the requirements for the Doctor of Philosophy at the University of Edinburgh. I certify that the work presented in this thesis is, to the best of my knowledge and belief, original, except as acknowledged in the text, and that the material has not been submitted, either in whole or in part, for a degree at this or any other university.

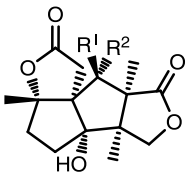
Naim Nazef

Abstract

Merrilactone A (**1**) and the epimeric anislactones A (**2**) and B (**3**) are sesquiterpene natural products that were first isolated from the dried pericarps of *Illicium merrillianum* (Fukuyama in 2000) and *Illicium anisatum* (Kouno in 1990), respectively. Merrilactone A (**1**) was identified as a potent nonpeptidal neurotrophic factor that strongly promotes neurite outgrowth in the culture of foetal rat cortical neurons and is a potential small molecule lead for the treatment of neurodegenerative disorders. Merrilactone A (**1**) together with **2** and **3**, are highly complex cage-like structures that have established themselves as challenging and attractive targets in natural product synthesis.



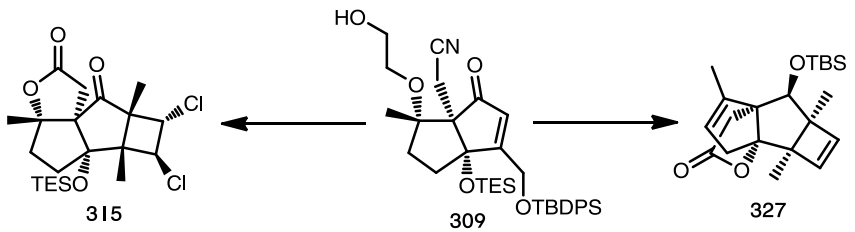
Merrilactone A, **1**



Anislactone A, **2**. R^1 = H, R^2 = OH

Anislactone B, **3**. R^1 = OH, R^2 = H

Presented in this research is a regiodivergent approach to both sets of natural products via the first known application of the defining transformation, an intramolecular tandem cyano-aldol cyclisation. We demonstrated an efficient route to the cyano-aldol product **303**, which acted as the common intermediate to either natural product by orthogonal lactonisation sequences. This culminated in the successful synthesis of known intermediate **320**, which represents the formal total synthesis of **1**, and advanced tetracyclic intermediate **309**, that is the full carbon skeleton of **2** and **3**.



315 **309** **327**

Acknowledgements

During the course of a PhD, you learn more about yourself and life than you do chemistry.

This is a notion I joked about with my colleagues in the Greaney group over the last four years. Without a doubt, my chemical knowledge has increased, but my research also taught me invaluable personal lessons that I will always keep with me, in and out of the lab: how to be tenacious during even the most trying moments and to give yourself time to re-assess direction and approach.

I would like to thank my advisors, Dr. Mike Greaney and Dr. Rob Davies. Their passion and vision for chemistry have inspired me to become a better researcher. In particular, I would like to express my gratitude to Mike for entrusting me with this project, sharing his knowledge and allowing me to create my own path throughout the PhD.

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I would like to thank the staff of the chemistry department for all their help with special acknowledgement to Juraj Bella for his assistance with NMR. Of course, without funding none of this would have sprung into life, and so I am grateful to EaStCHEM for the research scholarship and to AstraZeneca for the CASE award and warm welcome during my time at Alderely Park.

Finally, the overwhelming love and encouragement from my wife Jutika throughout my PhD, especially during periods of disappointment and despair, has reconfirmed how lucky I am to have her as my partner through life. We have had many warm memories of our time in Edinburgh, but none more precious than the

birth of our first child and son, Zavian. He has given me immense joy, love and the motivation to complete my PhD as soon as possible!

Contents

Abbreviations

Ac	acetyl
AD	Alzheimer's disease
AIBN	2,2-azobis(isobutyronitrile)
aq	aqueous
ASA	atmospheric solids analysis
Bn	benzyl
br	broad
BTB	*bis*-(trifluoromethyl)benzyl
Bu	butyl
Bz	benzoyl
calcd	calculated
cat	catalytic
COSY	correlation spectroscopy
Cp	cyclopentadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBB	di-*tert*-butylbiphenylide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DCB	2,6-dichlorobenzyl
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIBALH	diisobutyl aluminium hydride

DIPEA	*N,N*-diisopropylethylamine
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EOM	ethoxymethyl
Equiv/eq	equivalent
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
GABA	gamma-aminobutyric acid
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethyl phosphoric acid triamide
hr	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamine
LHMDS	lithium hexamethyldisilazide
M	molar (moles per litre)

m	multiplet
m/z	mass to charge ratio
MBH	Morita-Baylis-Hillman
***m*CPBA**	*meta*-chloroperbenzoic acid
Me	methyl
mins	minutes
MMPP	magnesium monoperoxyphthalate hexahydrate
MOM	methoxymethyl
mp	melting point
Ms	mesyl
MS	molecular sieves
MVK	methyl vinyl ketone
NaHMDS	sodium hexamethyldisilazide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
NTF	neurotrophic factor
°C	degree(s) Celsius
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Piv	pivaloate
PMB	*para*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
ppm	parts per million
q	quartet
RCM	ring-closing metathesis
RT	room temperature

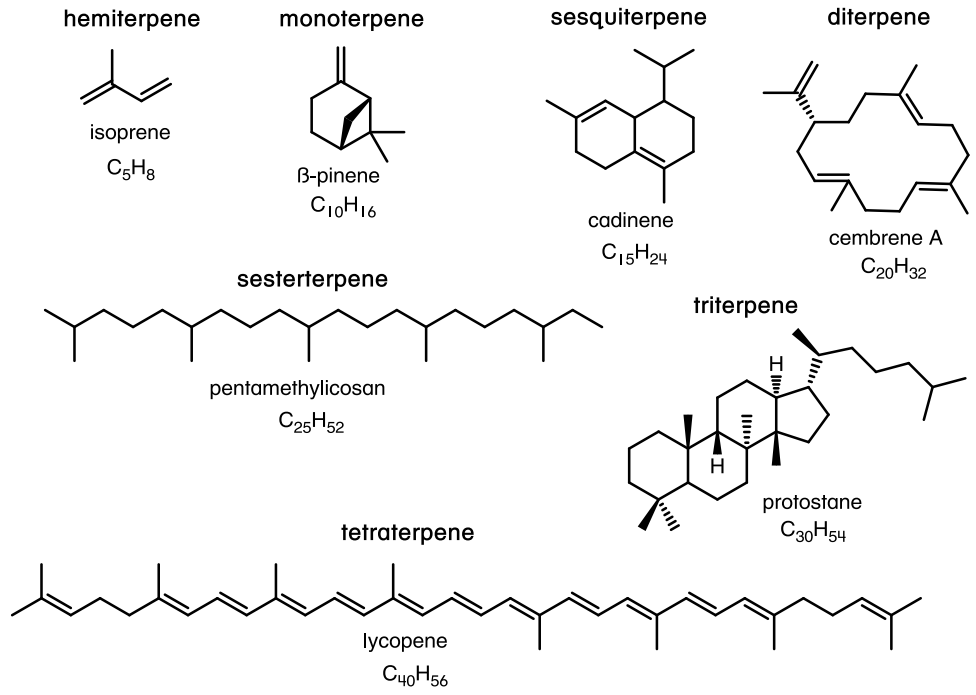
Sia	siamyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TCNQ	tetracyanoquinodimethane
TDS	thexyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	Triisopropylsilyl chloride
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl
UV	ultraviolet
δ	chemical shift

1 Introduction

1.1 *Illicium* Sesquiterpenes: Origin, Structure and Biosynthesis

Terpenes are the largest and most diverse class of natural products with over 55,000 compounds isolated to date. The colossal structural diversity offered by this class of secondary metabolites ensures an extensive range of biological properties—ranging from anti-cancer and anti-malarial activities, to tumor promotion and ion-channel binding. Terpenes are ubiquitous in nature and are used to defend many species of plants, animals and microorganisms against predators, pathogens and competitors. Apart from being used as a deterrent, terpenes are used as a communication tool to alert others to the presence of food, mates and enemies.[1] Derived biosynthetically from, and classified by, the number of isopropene units used to construct them, they have a basic molecular formula of $(C_5)_n$ otherwise known as the 'isoprene rule'.[2] Further rearrangement of the carbon skeleton and oxidation results in an almost endless amount of possible structures. These different classes include hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}) and polyterpenes ($> C_{40}$). Representative examples of compounds belonging to these classes of terpenes are shown in Figure 1-1.

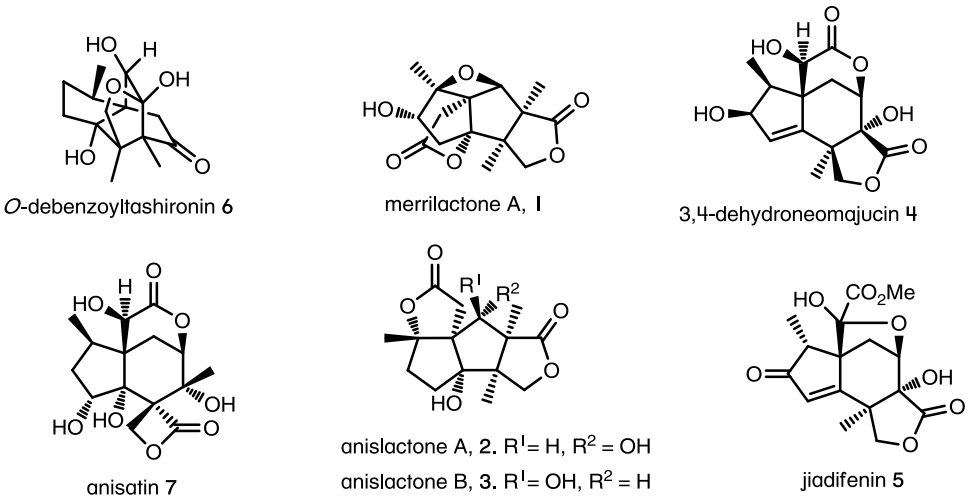
Figure 1-1: Representative examples of terpene natural products



Sesquiterpenes or sesquiterpenoids exhibit a 15-carbon skeleton resulting from the combination of three isoprene units. This group of natural products cover an immense range of structural diversity (over 200 skeletal types), which includes acyclic, monocyclic, bicyclic, tricyclic, tetracyclic and pentacyclic compounds. A rich source of sesquiterpenes can be found in the characteristic star-shaped fruits of *Illicium*, a genus of flowering plants, evergreen shrubs and trees indigenous to tropical and subtropical regions of North America, Mexico, the West Indies and eastern Asia. An abundance of these species are found in the northern regions of Myanmar and China, with 24 species considered native to China.[3,4] The fruits of *Illicium* are commonly known as 'Star Anise' and the Chinese star anise (*Illicium verum*) has a long history of use as a spice in cooking and as a herbal treatment for infant colic. In contrast, the fruits of *Illicium anisatum* are not consumed as they have been acknowledged for many centuries to contain toxic compounds, and it is well documented that they cause convulsions and serious neurological effects such as seizures, vomiting and jitteriness.

Numerous attempts to isolate the toxic ingredient of the *Illicium anisatum* plant were unsuccessful until 1952, when Lane isolated a pure toxic compound to which the name anisatin **7** was first proposed.[5] The structure of anisatin was later fully established in 1968 by Yamada and co-workers as a structurally unique sesquiterpene.[6] Anisatin is regarded as one of the most potent neurotoxins of plant origin (LD_{50} = 1 mg/kg, mice) and further neuropharmacological studies have revealed it to be a potent noncompetitive GABA antagonist.[7,8] The isolation of anisatin generated intense chemical interest into the components of the *Illicium* species culminating in the isolation and structural determination of several biologically active sesquiterpenes **4–6** and **1** (Figure 1-2).[4,9,10]

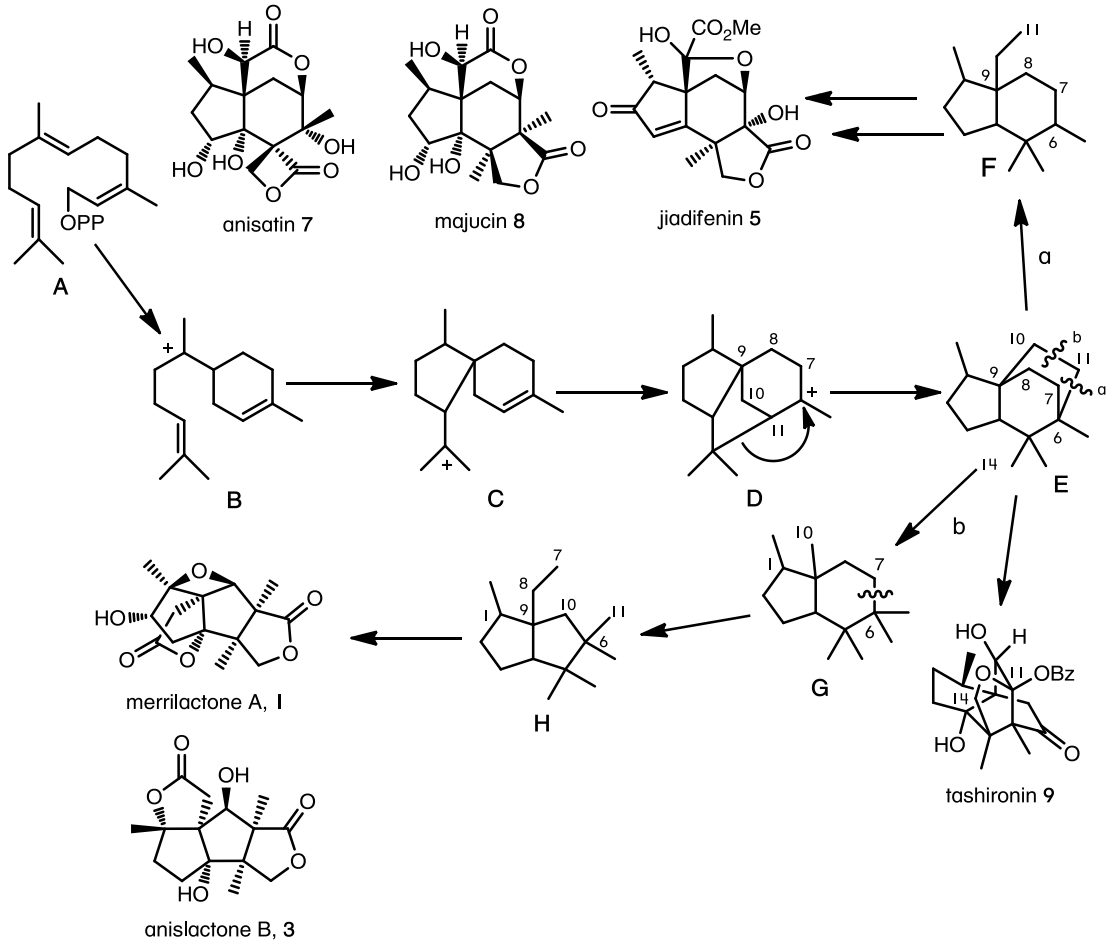
Figure 1-2: Examples of sesquiterpenes isolated from the *Illicium* species



Fukuyama and colleagues were responsible for the isolation of a large number *Illicium* sesquiterpene natural products **1–6** and demonstrated **1** and **5** to have potent neurite outgrowth activity in primary cultured rat cortical neurons.[4,11] These sesquiterpenes have attracted much attention for the development of small molecule neurotrophic factors as a possible treatment of neurodegenerative disorders such as Alzheimer's, Huntington's or Parkinson's disease.[9]

Even though the structures show great diversity in their fused-ring architectures, Fukuyama proposed that compounds **1-7** are biosynthetically related.[12] As illustrated in Scheme 1-1, Fukuyama suggested that compound **E** is a common intermediate that is derived from **A** via intermediates **B-D**. Compound **E**, which is tied to structure **4**, undergoes cleavage of bond *a* to provide **5**, **7** or **8** through **F**. Cleavage of bond *b* of **E** leads to bicyclic carbon skeleton **H** through **G**, leading to the biosynthesis of **1**, **2** and **3.**

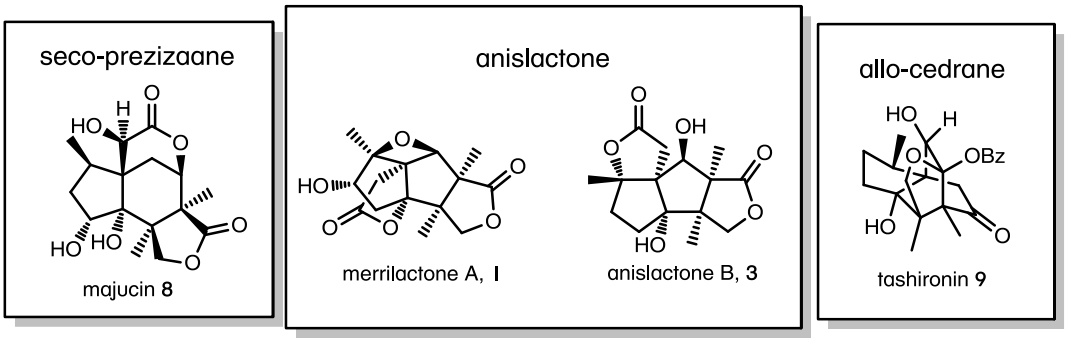
Scheme 1-1: Proposed biosynthetic route of sesquiterpenes from *Illicium* species



Illicium sesquiterpenes, based on their carbon skeletons, have been classified into three groups: seco-prezizaane, anislactone and the very rare allo-cedrane types.[13,14] The majority of *Illicium* sesquiterpenes belong to the seco-prezizaane group, which is divided further into four sub-groups according to their carbon architecture:

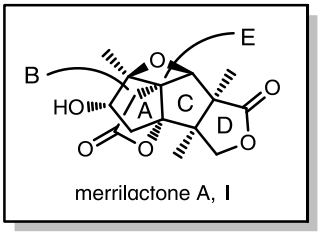
anisatin **7**, pseudoanisatin, majucin and minwanensin types.[4] Majucin **8**, merrilactone A (**1**), anislactone B (**3**) and tashironin **9** are representative structures of the three main groups (Figure 1-3). These occur exclusively in the *Illicium* species and are considered to be characteristic chemical markers of this species of plants. Many of these compounds have unique and complex carbon frameworks consisting of various fused-ring structures and dense stereochemical congestion.[15] This, combined with the interesting neurotrophic behaviour of a number of these, has attracted the attention of daring synthetic organic chemists as noteworthy targets for total synthesis.

Figure 1-3: Representative compounds of the three main structural groups of *Illicium* sesquiterpenes



1.2 Merrilactone A, Anislactones A and B: *Origin, Structure and Properties*

1.2.1 Merrilactone A



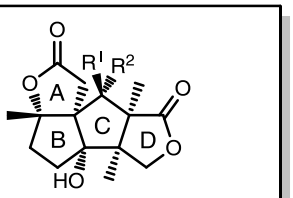
merrilactone A, **1**

Plants of the *Illicium* species have generated much chemical interest as they are a rich source of rare bioactive sesquiterpenes. The species *Illicium merrillianum*, abundant in parts of China and Myanmar, has alone had more than 36 structurally unique sesquiterpenes isolated from them.[16] In the search of non-peptidic neurotrophic compounds by Fukuyama and co-workers, merrilactone A (**1**)[†] was first isolated in 2000 from the methanol extract of the pericarps of *Illicium merrillianum* in an overall yield of 0.004% yield.[11] Structural determination of merrilactone A was achieved using a combination of spectroscopic and X-ray data analysis with the absolute configuration confirmed by Mosher's method. The structure confirmed merrilactone A to be an anislactone-type sesquiterpene with a pentacyclic caged structure, with two δ-lactones and a unique oxetane bridge, which at the time was the first known example of an anislactone-type sesquiterpene containing an oxetane ring. The dense, highly oxygenated compact architecture also contains seven contiguous stereocentres of which five are fully substituted carbons and a *cis*-arrangement of two angular methyl groups at the CD ring junctions. This demanding steric congestion will challenge modern synthetic methodology and stereoselective C–C bond formation. Biological assessment revealed intriguing neurotrophic activity, promoting neurite outgrowth in the primary cultures of foetal rat cortical neurons at concentrations of 0.1- 10 μM, confirming merrilactone A to be a possible lead compound for the development of novel

[†] An inconsistency in the labelling of the five rings of merrilactone A (**1**) is evident in the literature. Several different systems of labelling are in use, however, all labelling employed within this document is based on the assignment shown here.

nonpeptidal neurotrophic factors as a treatment for neurodegenerative disorders.[11] This combination of structural complexity and intriguing biological activity has made this challenging synthetic target spark the attention of numerous research groups. This has culminated in a total of five total syntheses by the research groups of Danishefsky,[17,18] Inoue and Hirama,[19-21] Mehta,[22] Frontier,[23,24] and Greaney,[25] in addition to several synthetic studies on subsections of the merrilactone A framework.[26-29]

1.2.2 Anislactones A and B



anislactone A, **2** R^1 = H, R^2 = OH
anislactone B, **3** R^1 = OH, R^2 = H

Anislactones A (**2**) and B (**3**)[‡] were first isolated from the methanol extracts of dried pericarps of *Illicium anisatum* by Kouno and co-workers in 1989 and 1990, respectively. They were both obtained in an overall yield of 0.0003% and their structures established by the use of NMR analysis combined with extensive spectroscopic and X-ray crystallographic methods.[30-32] Interestingly, anislactone B was later isolated as the main component of the fruits of *Illicium merrillianum* in an overall yield of 0.18% (over 600 times more abundant than in *Illicium anisatum*).[15] At the time of their discovery, their unique carbon skeleton structures had never been found before in nature. This led to the creation of a new class of sesquiterpene, aptly named 'anislactone-type'.

Anislactones A and B, are a pair of epimeric sesquiterpenes that have a remarkable and intricate structure with an unusual tetracyclic carbon skeleton with two γ-lactones and six stereocentres, of which five are contiguous fully substituted carbon centres. Unlike merrilactone A, anislactones A and B have received little

[‡] All labelling of the four rings of anislactones A (**2**) and B (**3**) within this document are based on the assignment shown here.

interest from synthetic research groups largely because of their unknown biological activity with only a single total synthesis reported to date.[25] Nevertheless, these structurally complex epimers are synthetically challenging, present an interesting platform to showcase new C–C bond forming methodologies and are attractive targets in natural product synthesis.

1.3 Biological Activity: *Neurotrophic Factors and Alzheimer's Disease*

Neurotrophic factors (NTFs) are small proteins that have the ability to promote nerve cell survival and to maintain and/or enhance nerve cell function. NTFs regulate growth of neurons, associated metabolic functions such as protein synthesis, and the ability of the neuron to make neurotransmitters. This allows the neuron to communicate with other neurons or with other targets (e.g. skeletal muscle). Because of these actions, neurotrophic factors play a significant role in the maintenance of neuronal function throughout an individual's entire lifetime. Neurons that fail to obtain the necessary NTFs die by a process called programmed cell-death. Alterations in the levels of NTFs, due to age, genetic background or other factors might contribute to neuronal degradation processes. Based on this evidence, it has been postulated that a diminished endogenous neurotrophic support may lead to neuronal degeneration, characteristic of neurodegenerative diseases like Alzheimer's, Parkinson's and Huntington's disease. Therefore, NTFs are attractive candidates as therapeutic agents for neurodegenerative disorders and acute injuries including trauma and stroke.[33]

Alzheimer's Disease (AD) is a common, insidiously progressive form of dementia that affects memory, thinking and behaviour. Dementia affects 825,000 people in the UK with AD accounting for more than 50% of that number and 25 million (or 45%) of the UK population has a close friend or family member affected by dementia. Dementia now costs the UK economy more than £23 billion a year—more than cancer and heart disease combined.[34] AD is characterised by confusion,

irritability and aggression, mood swings, language breakdown, long-term memory loss and the general withdrawal of the sufferer as their senses gradually deteriorate. AD is an irreversible process and currently used treatments offer a small symptomatic benefit; no treatments to delay or halt the progression of the disease are, as of yet, available. As of 2011, more than 800 clinical trials in the US have been conducted for identification of a promising treatment for AD, but it is unknown if any of these will show promising results.[35] Current research have proposed numerous hypotheses for the onset of AD, yet most present drug therapies are based upon the cholingenic hypothesis.[36]

The two main pathological markers in people affected by AD are:

- *Amyloid plaques*. Plaques contain ß-amyloid (Aß) peptides which are made by a protein called amyloid precursor protein. These plaques are dense insoluble deposits and also contain cellular material outside and around neurons. The accumulation of Aß has been associated with neuronal damage and the weakening of synaptic connections important for memory formation. Until recently, it has been assumed that amyloid plaques were the primary cause of neuronal damage in AD. Recent developments have revealed soluble forms of ß-amyloid which are now thought to be the main culprits in neuronal damage.[37-39]
- *Neurofibrillary tangles.* These are found inside neurons and are abnormal aggregates of a protein called *tau*. *Tau*-protein binds to microtubules and helps stabilise them preserving the transport of nutrients to the end of the axon, and maintaining the overall health of the neuron. In AD, *tau* undergoes abnormal chemical changes causing it to disengage from microtubules and self-aggregate to form neurofibrillary tangles. The microtubules disintegrate, and the neuron's transport system collapses.[37]

The use of acetylcholinesterase inhibitors as treatments for AD has been met with limited success and intracerebroventricular administration of NTFs to reverse neuronal atrophy are now becoming promising alternatives. Infusion of nerve growth factor into aged rats and primates reduced the spatial recent memory deficits making this a possible treatment for AD.[40] Common to all peptides is their inherent metabolic instability to oral administration and poor cell penetration properties, making the less convenient route of intravenous administration the only way of ensuring sufficient drug levels reach the brain. Small molecule non-peptide based neurotrophic agents are expected to be stable alternatives to NTFs, and thus are promising therapeutic agents. Exploration in the development and preparation of such agents will contribute to the understanding and eventual effective treatment of neurodegenerative diseases.[41]

1.4 Previous Total Syntheses of Merrilactone A

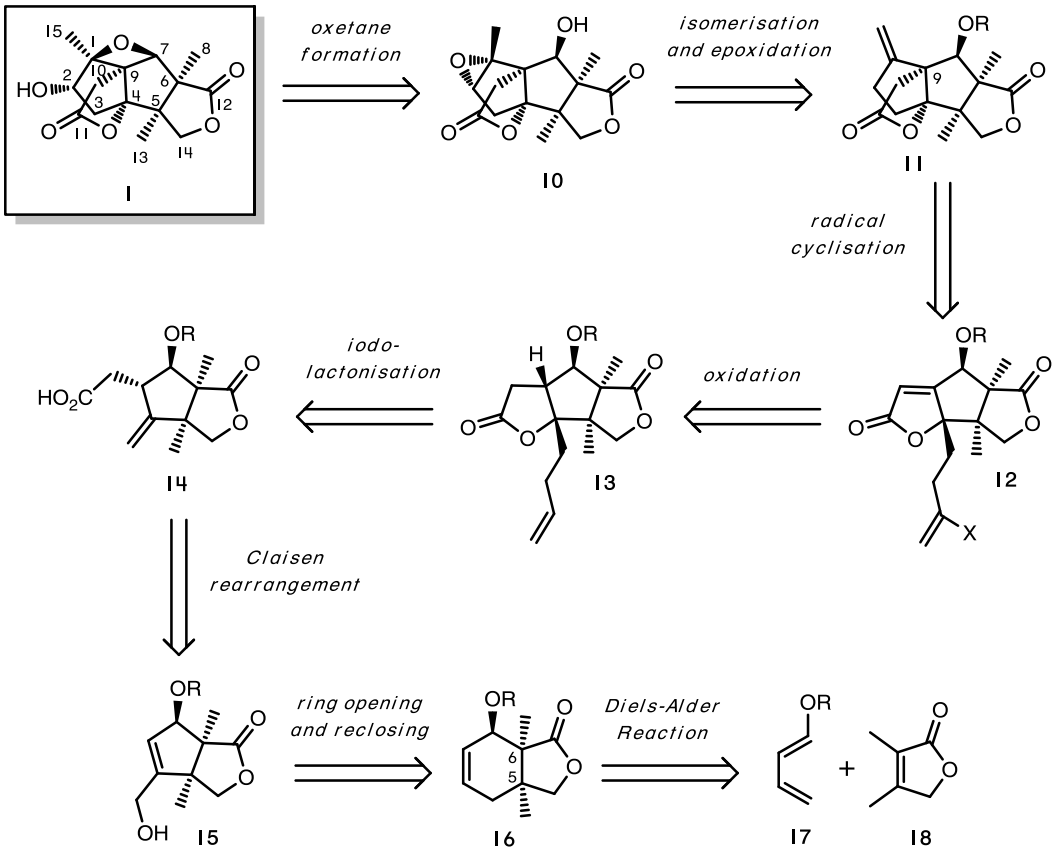
Merrilactone A has attracted considerable attention from research groups due to its conceivable use as a lead compound for the development of nonpeptidal small molecule drugs towards the treatment of neurodegenerative disorders. The highly complex pentacyclic carbon skeleton with a cage-like structure added to its attractiveness, establishing merrilactone A as a challenging target for total synthesis.

1.4.1 Danishefsky's total syntheses of Merrilactone A

1.4.1.1 Racemic total synthesis

In 2002, the Danishefsky group reported the first total synthesis of (±)-merrilactone A (**1**). This efficient racemic synthetic approach yielded merrilactone A in an overall yield of 10.7% over a very respectable 20 steps but still left room for improvement, as several transformations lacked regio- and stereoselective control.[17] The planned retrosynthesis is outlined in Scheme 1-2.

Scheme 1-2: Danishefsky's retrosynthetic analysis of merrilactone A

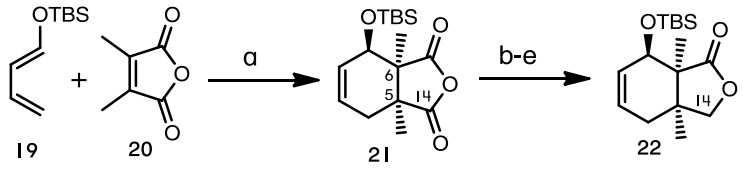


The oxetane linkage is installed in the last step via a known biomimetic homo-Payne-type rearrangement of epoxy alcohol **10**. The C1 oxygen functionality is introduced by epoxidation after isomerisation of *exo*-methylene **11**,[12] and the sterically crowded C9 quaternary centre would be installed via an ambitious radical cyclisation of **12**. Tricycle **12** was in turn envisioned to be obtained via a two-fold oxidation of **13**, which could arise from the iodolactonisation of γ,δ-unsaturated acid **14**. Substrate **14** was expected to be prepared by a Claisen rearrangement from allylic alcohol **15**, which itself could be accessed by ring contraction of the 6-membered ring in **16**. Diels–Alder reaction of diene **17** and dienophile **18** was intended to establish the contiguous quaternary stereocentres at C5 and C6.[9]

The synthesis opened with a Diels-Alder reaction between diene **19** and 2,3-dimethylmaleic anhydride **20** furnishing adduct **21** in 74% yield. This simple, but powerful cycloaddition reaction under stereo- and regioselective control established

the stereochemistry of three stereocentres, installing both *cis*-methyl groups at newly formed quaternary centres C5 and C6 (Scheme 1-3).

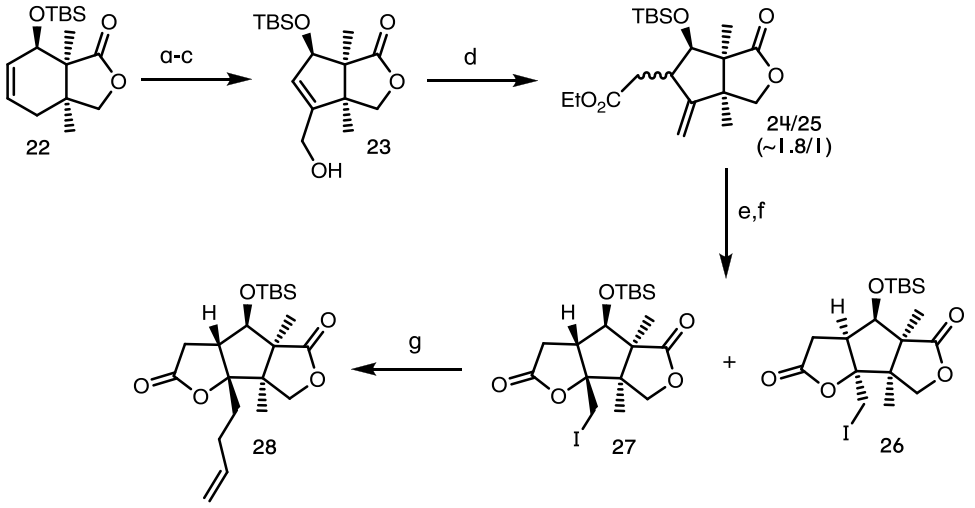
Scheme 1-3: Diels Alder reaction and regioselective C14 reduction



a) 165 °C, mesitylene, 74%; b) NaOMe, MeOH; c) $ClCO_2Me$, THF, then $NaBH_4$, MeOH, –35 °C; d) aq. LiOH; e) $LiBHEt_3$, THF, then TFA, DCM, 78% (four steps).

Attempted reductions at the C14 carbon using conventional reducing agents led to complex mixtures and as a result, a laborious but high-yielding four-step sequence was employed, affording **22** in 78% yield from **21**. An overall ring contraction was performed next, starting with ozonolysis of **22**, followed by treatment with triphenylphosphine leading to the *bis*-aldehyde, which after aldol condensation and reduction of the αß-unsaturated aldehyde, afforded the newly formed five-membered ring in **23** in high yield (Scheme 1-4).

Scheme 1-4: Johnson-*ortho*-ester reaction and Keck *C*-allylation

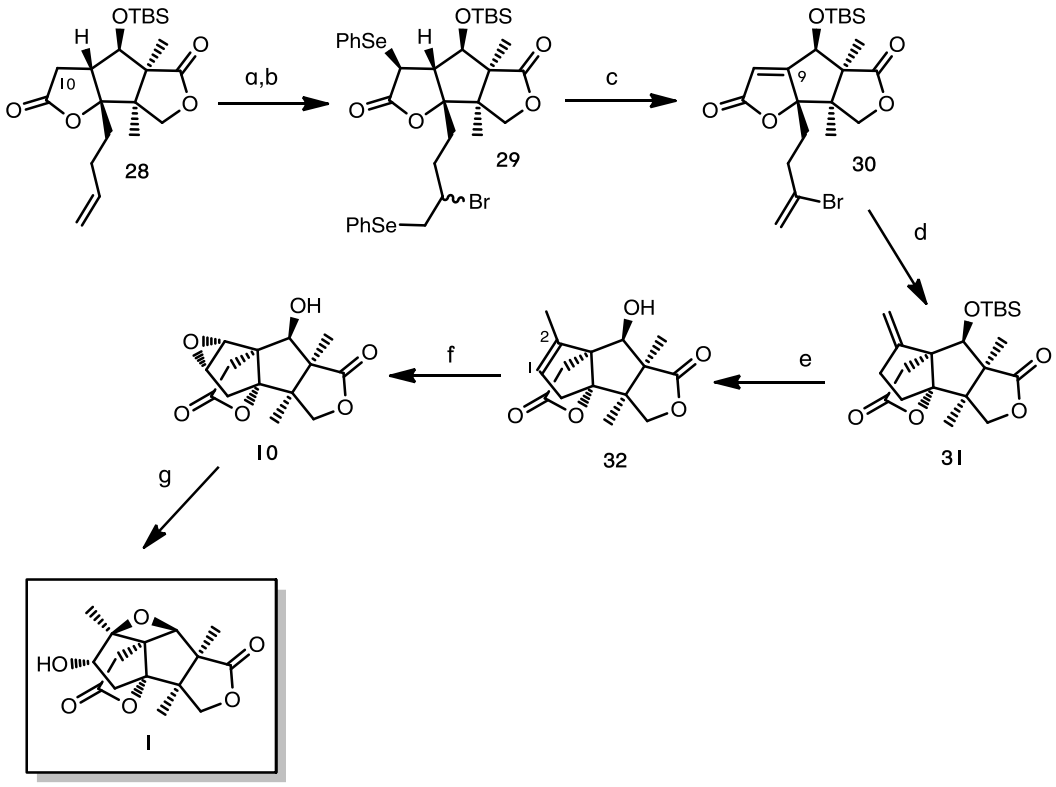


a) O_3, PPh_3, DCM/MeOH; b) $Bn_2NH{\cdot}TFA$, PhH, 65 °C, 94% (two steps); c) $NaBH_4$, DCM, MeOH, –78 °C, quant.; d) $MeC(OEt)_3$, mesitylene, PivOH, 135 °C, 92%; e) aq. LiOH, MeOH; f) I_2, $NaHCO_3$, THF, 59% **27** and 35% **26** (two steps); g) $AllylSnBu_3$, AIBN, PhH, 75%.

Johnson-Claisen rearrangement of **23** resulted in the formation of diastereomeric mixture of esters **24/25** in a ~1.8:1 ratio. After hydrolysis of the ester mixture and subsequent iodolactonisation of the resulting acids, two chromatographically separable iodolactones **26** and **27**, were obtained, in 35% and 59% yield, respectively. Chain extension of **27** was accomplished by the Keck C-allylation method to give tricyclic intermediate **28**.

Synthesis of the key radical cyclisation substrate was achieved by a two-fold oxidation sequence. Selenylation of lactone **28** at C10 via an intermediate silyl ketene acetal was followed by bromoselenylation of the terminal vinyl group, resulting in the *bis*-selenide **29**. Oxidation-induced deselenation afforded the desired **30** in an overall yield of 77% from **28** over three steps. The decisive radical cyclization of vinyl bromide **30** delivered the desired tetracyclic core **31** whilst overcoming extreme steric congestion at the sp^2 centre at C9. Isomerisation of the *exo*-olefin into the ring and simultaneous alcohol deprotection supplied ß-alcohol **32** in 98% yield. Hydroxyl groups have often been used with peracids to direct epoxidation in a *syn* sense[42] but in this specific situation, the congested nature of the *β*-face of the C1–C2 double bond was sufficient for the epoxidation to mainly occur from the α-face (α/β epoxide = 3.5:1). To complete the total synthesis, an acid induced *homo*-Payne rearrangement of the major isomer **10** installed the final oxetane ring generating merrilactone A (Scheme 1-5).

Scheme 1-5: Final stages of the synthesis of merrilactone A including free radical cyclisation and *homo*-Payne rearrangement



a) LHMDS, TMSCl, PhSeCl; b) PhSeBr, MeCN; c) O_3, DCM, 1-hexene, PhH, NEt_3, reflux, 77% (three steps); d) Bu_3SnH, AIBN, PhH, 90%; e) $TsOH{\cdot}H_2O$, PhH, reflux, 98%; f) *m*CPBA, DCM, 3.5:1 ratio of α /β epoxide, quant.; g) $TsOH{\cdot}H_2O$, DCM, 71% (two steps).

This highly efficient synthesis of (±)-merrilactone A had set the bar high for future syntheses of the natural product. Even more impressive is the fact that this synthesis was completed only two years after the characterisation of the natural product, but even so, a number of selectivity issues have been left unresolved.

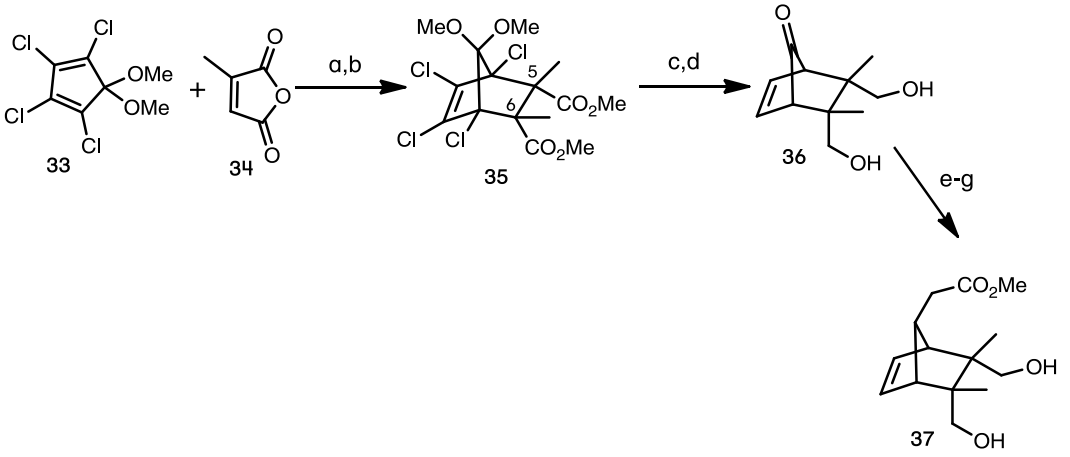
1.4.1.2 Asymmetric formal synthesis

In an effort to address the regio- and diastereoselectivity issues in his earlier racemic synthesis of merrilactone A, Danishefsky and co-workers reported in 2005, an improved formal, asymmetric synthesis to either enantiomer of the natural product.[18] Stereocontrolled synthesis of key intermediate **27** was deemed to be a significant milestone in this new approach as the transformations from **27** to

merrilactone A were already proven to be concise and efficient.[17] A re-work was required on the synthetic steps to enantiomerically pure **27**, such as the regioselective C14 reduction to **22** that required a lengthy four step circumvention, or the marginally selective Claisen rearrangement, yielding a mixture of diastereomeric esters **24/25** in a less than optimal ~1.8:1 ratio (Scheme 1-4).

The synthesis opened with the *endo*-selective Diels-Alder reaction between diene **33** and cyclic anhydride **34**, installing the C5 quaternary centre. Subsequently, methanolysis of the anhydride, esterification of the free acid, followed by a stereoselective methylation via lithiation installed the C6 quaternary centre and afforded *meso*-**35** in 87% yield over two steps. A stepwise LAH and Birch reduction of **35** yielded ketone **36**, which after protection as the acetonide, Horner–Emmons olefination, Mg-promoted 1,4-reduction and removal of the acetonide supplied *meso*-diol **37** an overall yield of 48% over five steps (Scheme 1-6).

Scheme 1-6: *Endo*-Diels Alder and conversion into *meso* 1,4-diol compound **37**

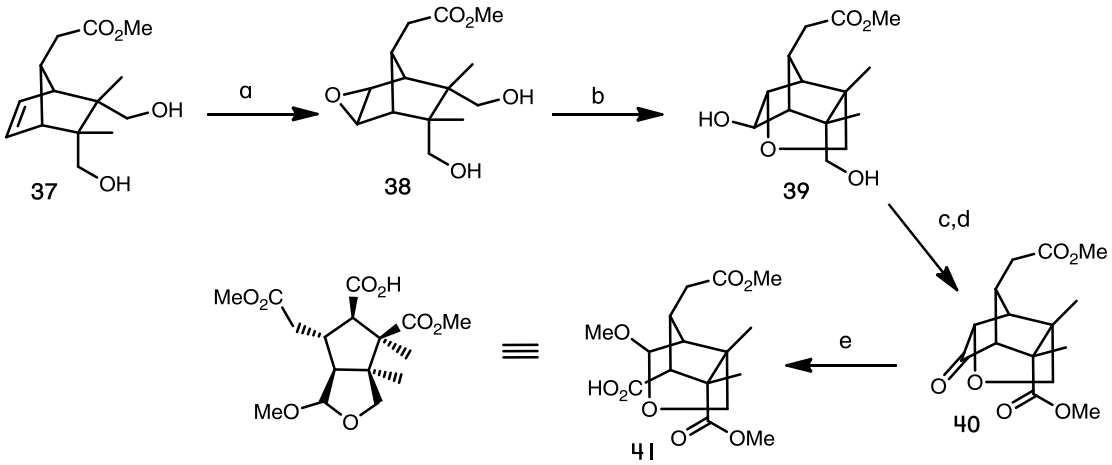


a) 180 °C, neat, then MeOH, reflux, PhH/MeOH, $TMSCHN_2$. 92%; b) LDA, HMPA, MeI, THF, –78 °C to RT, 95%; c) $LiAlH_4$, THF, reflux; d) Na, NH_3, THF/EtOH, 72% over 2 steps; e) 2,2-dimethoxypropane, acetone, TsOH; f) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 86% (two steps); g) Mg, MeOH, 77%.

To achieve an enantioselective synthesis of merilactone A, a crucial asymmetric epoxide-ring-opening reaction was utilised. DMDO epoxidation of *meso*-diol **37** led to *exo*-epoxide **38**, the substrate for the asymmetric ring-opening reaction. Treatment of **38** with a catalytic amount of (*S,S*)-[Co^{III}(salen)]-OAc as described by

Jacobsen and colleagues, yielded enantioenriched **39** with 86% ee and 86% yield.[43] As expected, use of the *R,R* Jacobsen catalyst led to *ent*-**39** allowing access to both enantiomers of merrilactone A. PDC oxidation of diol **39** followed by esterification gave ketoester **40** in a 70% yield over two steps. A Baeyer-Villiger oxidation converted **40** into bicyclic **41** in 88% yield (Scheme 1-7).

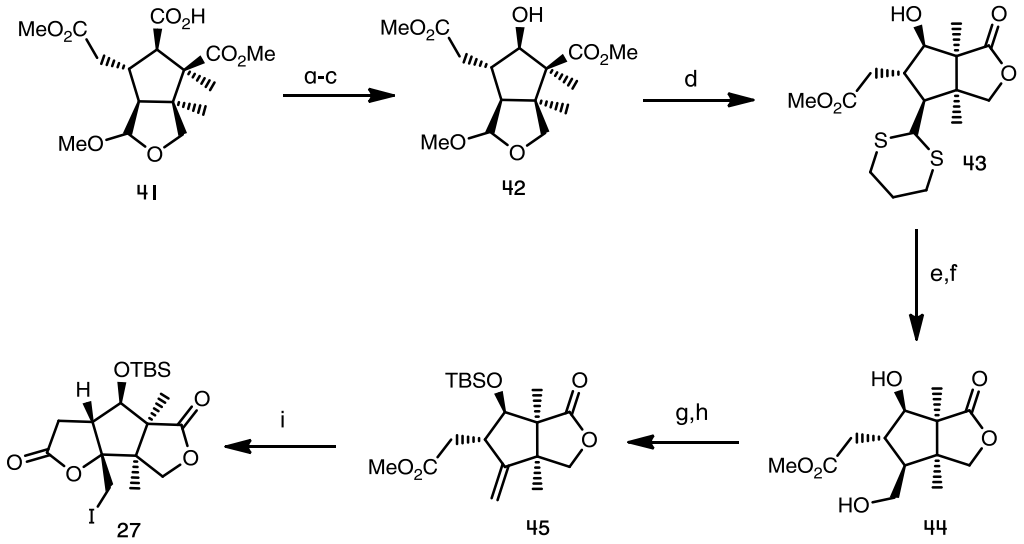
Scheme 1-7: Regio- and enantio-controlled chemical degradation pathway



a) DMDO, DCM; b) (*S,S*)-[Co^{III}(salen)]-OAc, –78 °C to –25 °C, THF, 86% (two steps); c) PDC, DMF; d) K_2CO_3, MeI, acetone, reflux, 70% (two steps); e) MMPP, MeOH, 0 °C to RT, 88%.

Carboxylic acid **41** was then transformed over three steps into the secondary alcohol **42** with retention of stereochemistry via carboxy inversion in an overall yield of 58% (Scheme 1-8). A Lewis acid facilitated ring opening of the methoxytetrahydrofuran ring moiety **42** by trapping its masked aldehyde, which resulted in lactonisation and produced **43**. The latter was then easily converted, via a two-step sequence, to diol **44**. With the synthesis of key intermediate **27** almost within reach, diol **44** was exposed to the protocols of Grieco, resulting in a selective reaction at the primary alcohol to provide a transient selenide, which afforded the desired *exo*-methylene **45** after oxidative elimination. Hydrolysis of **45** resulted in a carboxylic acid that underwent iodolactonisation to afford advanced intermediate **27** in a more efficient manner as compared to Danishefsky's first generation synthesis with an overall yield of 6% over 21 steps.[17]

Scheme 1-8: Completion of the synthesis of enantioenriched intermediate **27**



a) DCC, *m*CPBA, 0 °C to RT, 83%; b) PhH, reflux; c) K_2CO_3, MeOH, 70% (two steps); d) $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$, DCM, 50%; e) $PhI(OCOCF_3)_2$, $MeCN/H_2O$, 50%; f) $NaBH_4$, MeOH, 0 °C; g) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, then 30% H_2O_2, 86% (two steps); h) TBSOTf, NEt_3, DCM, 76%; i) LiOH, H_2O/MeOH, then I_2, aq. $NaHCO_3$/THF, 75%.

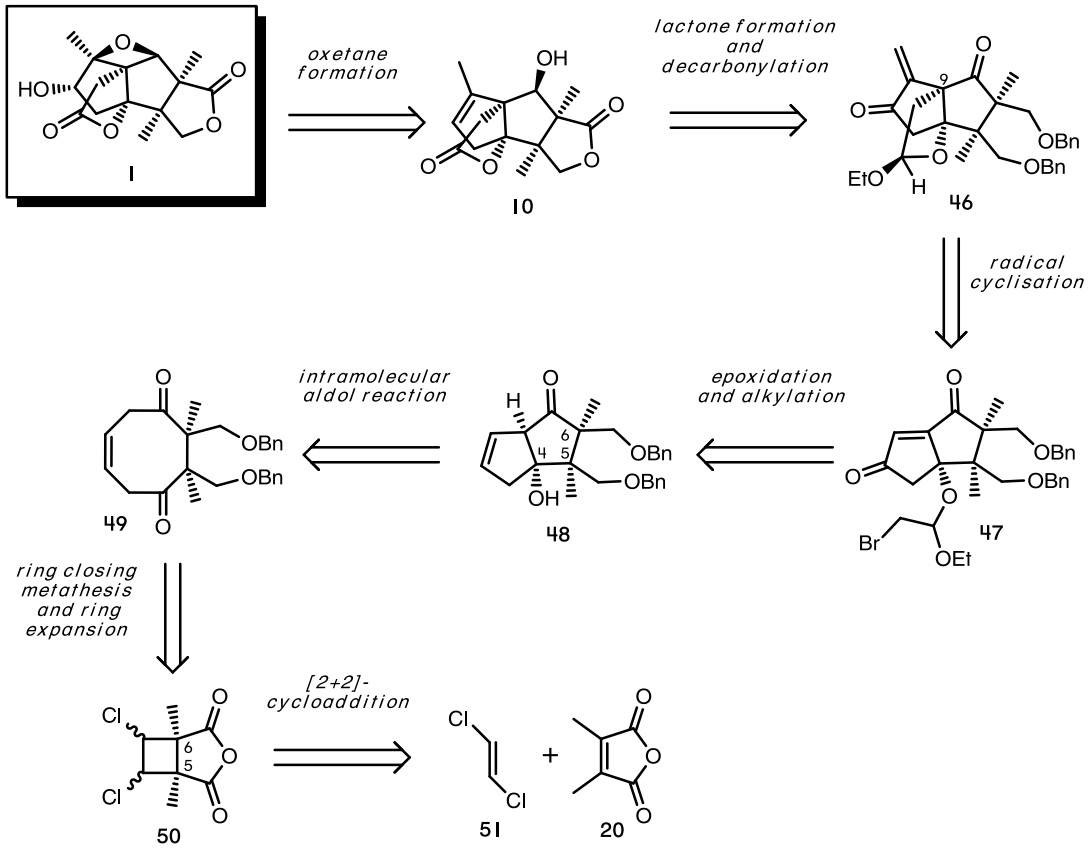
Advanced enantioenriched key intermediate **27** could then be converted to merrilactone A in eight steps via the same methods originally reported by the group in their racemic synthesis.[17] This revamped synthetic route addressed the selectivity issues highlighted by Danishefsky in his first generation synthesis and for the first time allowed access to either enantiomer of the natural product in 29 steps, concluding the first formal asymmetric synthesis of (-)-merrilactone A.

1.4.2 Hirama's total syntheses of Merrilactone A

1.4.2.1 Racemic total synthesis

In 2003, the Hirama group published the second total synthesis of merrilactone A.[19] In this racemic synthesis, a novel intramolecular aldol reaction of an eight-membered diketone was employed to construct the bicyclic core of merrilactone A. This innovative strategy completed the racemic total synthesis in 27 steps with an overall yield of 1% (Scheme 1-9).

Scheme 1-9: Hirama's retrosynthesis of merrilactone A

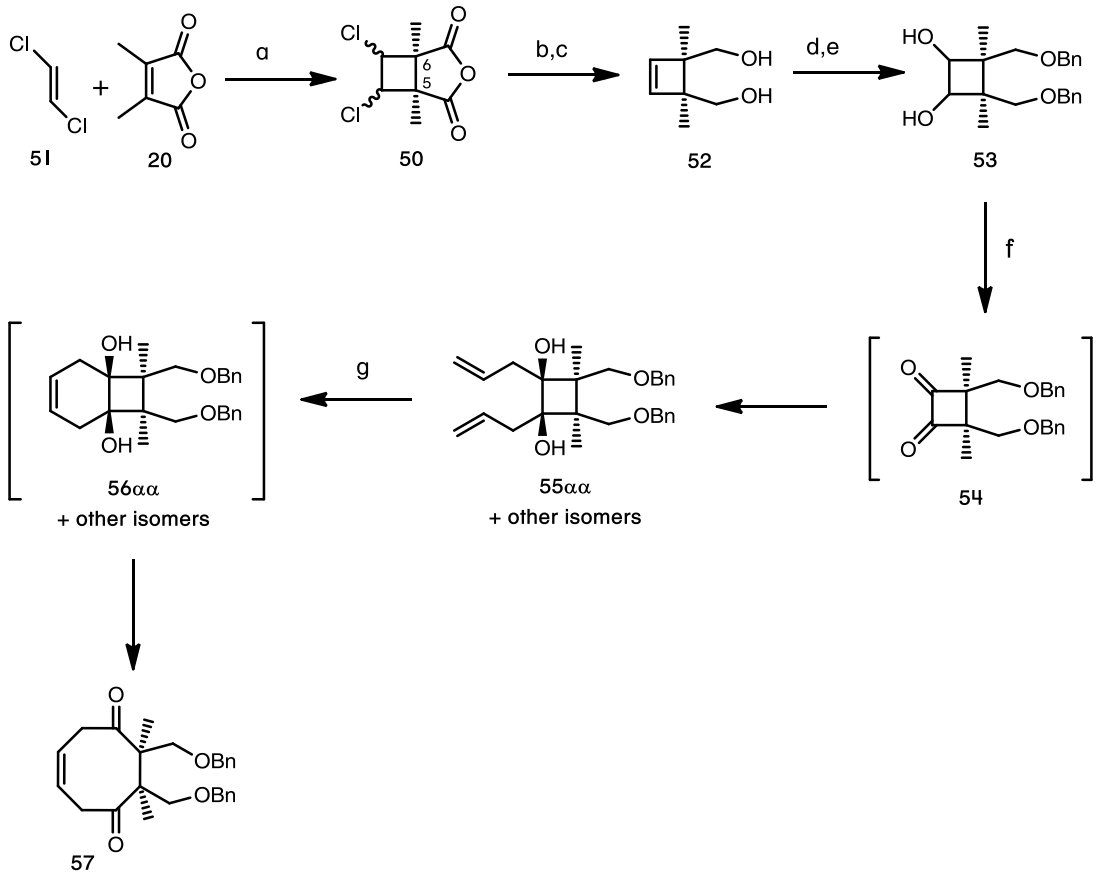


As previously demonstrated by Danishefsky, the *homo*-Payne rearrangement would once again be used to install the oxetane ring in the final step of the synthesis and give merrilactone A from precursor **10**. Tetracyclic **10** would be prepared from *exo*-methylene **46** via standard manipulations, which itself is envisaged to be obtained from bromo acetal **47** by the way of an intramolecular radical cyclisation, establishing the stereochemistry of the C9 quaternary centre. Simple manipulations of bicyclic **48** including epoxidation and alkylation would provide the bromo acetal **47**, substrate for the key radical reaction. The *cis*-bicyclo[3.3.0]octane core of **48** was expected to be accessible via a desymmetrisation of *meso*-diketone **49** by implementing a critical intramolecular aldol reaction. This single step would set the relative stereochemistries of three stereocentres, C4, C5 and C6. The substrate **49** for this key transformation would be the product of a number of relatively straightforward functional group manipulations, a double allylation and a ring closing

metathesis and ring expansion sequence from cyclobutane **50**. The two contiguous quaternary carbons at C5 and C6 would be introduced using a [2+2] cycloaddition reaction between *trans*-dichorloethylene **51** and cyclic anhydride **20**.[9]

In the forward synthesis, [2+2] photocyclisation between substrates **51** and **20** stereospecifically installed the consecutive C5 and C6 stereocentres (Scheme 1-10). Reductive dehalogenation of **50** and subsequent LAH reduction of the anhydride yielded *meso*-diol **52**, which was protected with benzyl ethers, and then subjected to OsO_4 induced dihydroxylation to afford **53** in a 44% yield over 5 steps. Swern oxidation of diol **53** and double-allylation of the resultant diketone **54** was accomplished in one-pot because of the strong tendency of diketone **54** toward hydration in the aqueous workup. The double *cis*-allylation of diketone **54** approached mainly from the α-face yielding a mixture of isomers of **55**. Ring-closing metathesis of **55αα** in the presence of Grubbs I catalyst effectively provided bicyclo[4.2.0]octane system **56αα** as the major isomer, which was subsequently treated *in situ* with $Pb(OAc)_4$ to furnish the eight membered ring system **57** in a 95% yield.

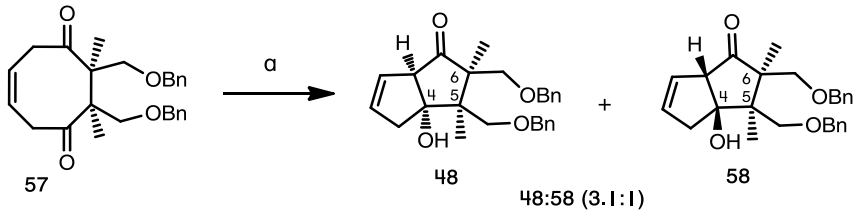
Scheme 1-10: Synthesis of *meso*-eight-membered diketone



a) benzophenone, acetone, hv; b) Zn dust, TMSCl, Ac_2O, toluene, 85 °C; c) $LiAlH_4$, THF, 47% (three steps); d) BnBr, NaH, THF/DMF, 99%; e) OsO_4, NMO, ^{t}BuOMe/^{t}BuOH/H_2O, 94%; f) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, then allylmagnesium bromide, –78 °C, 78% (**55αα**:**55ββ**:**55αβ**=15:2.6:1); g) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, then $Pb(OAc)_4$, RT, 95%.

Next followed the highlight of the total synthesis, a base-mediated intramolecular aldol reaction of meso-diketone **57**, which led to the selective formation of diastereomers **48** and **58**, whilst setting the relative stereochemistries of C4, C5 and C6 (Scheme1-11). The selectivity of this reaction was dependent on the conditions employed with the most optimal selectivity achieved using LHMDS at -100 °C, yielding a 3.1:1 ratio of desired diastereomer **48** over the undesired **58** in a combined yield of 85%.

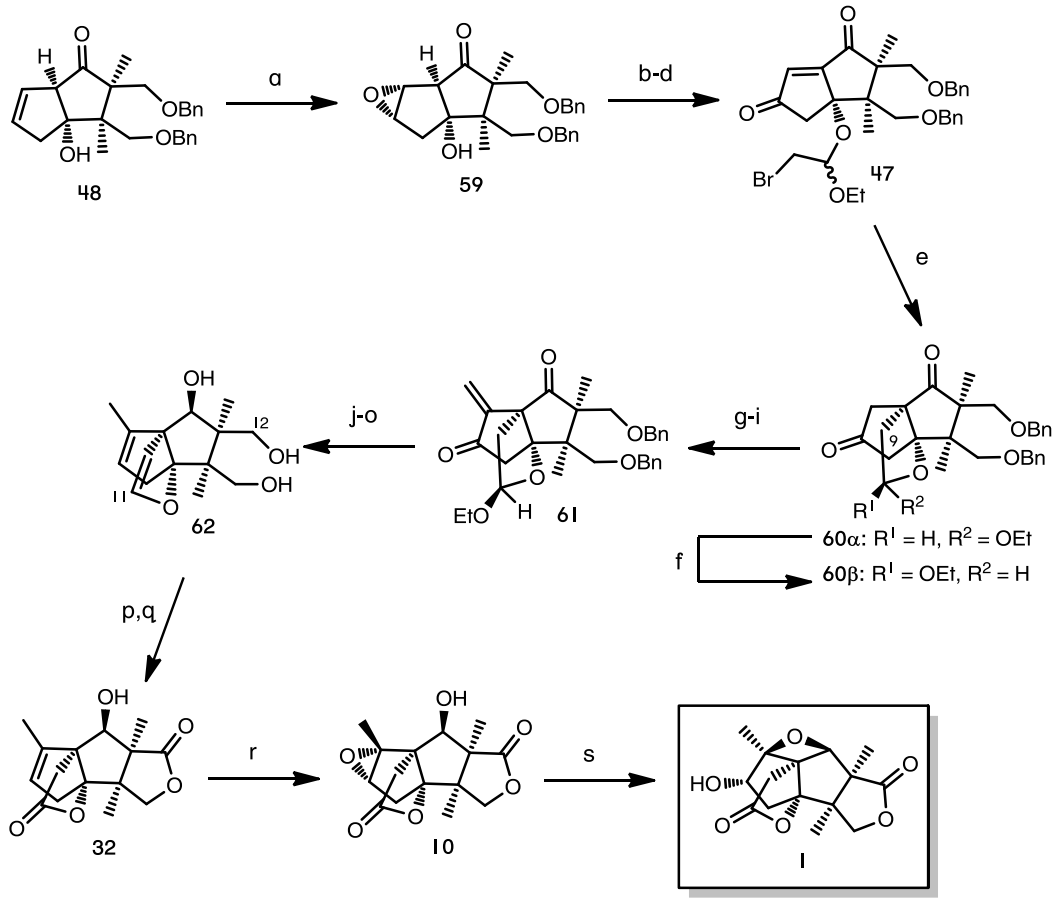
Scheme 1-11: Desymmetrisation via intramolecular aldol reaction



a) LHDMS, THF, –100 °C, **48:58**, d.r. ratio 3.1:1, 85%.

Epoxidation of the desired bicyclic product **48** afforded the α-epoxide **59**, which was subjected to a DBU-induced isomerisation and following IBX oxidation, an α-bromoacetal was appended to furnish **47** in 38% yield over four steps and as a 4:1 mixture of acetal diastereomers (Scheme 1-12). Radical cyclisation of the resultant diastereomeric mixture delivered 5-*exo* cyclised products **60ß** and epimeric **60α** in a 71% yield and diastereomeric ratio of 3.5:1(**ß:α**). Undesired diastereomer **60α** was easily converted to desired **60ß** under acidic ethanol conditions in an 86% yield. Tricycle **60ß** was then regioselectively transformed into *exo*-olefin **61** via a three-step sequence of TMSOTf, Eschenmoser's salt, followed by *m*CPBA induced elimination in an overall yield of 34%. Triol **62** was synthesised from *exo*-methylene **61** via a number of functional group conversions in which the order was critical for success. The subsequent enol ether of triol **62** was next hydrolysed and a simultaneous Fetizon oxidation of the C11 and C12 alcohols afforded tetracyclic **32** with astonishing regio- and chemoselectivity. The known two-step sequence of highly selective epoxidation from the α-face and an acid-induced *homo*-Payne rearrangement supplied merrilactone A (**1**).

Scheme 1-12: End sequence of the total synthesis of merrilactone A



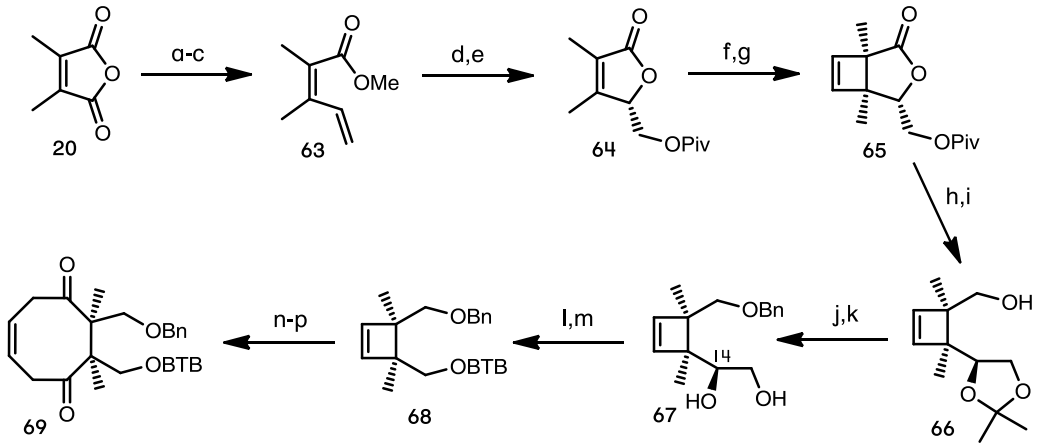
a) *m*CPBA, DCM, 81%; b) DBU, DCM, –40 °C , 81%; c) IBX, DMSO, 94%; d) $BrCH_2CHBr(OEt)$, $PhNMe_2$, DCM, –78 °C to RT, 62%; e) Bu_3SnH, BEt_3/O_2, toluene, 57% **60ß**, 16% **60α**; f) CSA, EtOH, RT, 86%; g) TMSOTf, DIPEA, DCM, –20 °C; h) $Me_2NCH_2^+I^-$, DCM; i) *m*CBPA, DCM, 70% (three steps); j) TFA/H_2O, 94%; k) MsCl, Et_3N, THF, 50 °C, 77%; l) $LiBH(s\text{-}Bu)_3$ (L-Selectride),THF, MS. 4Å, –78 °C then 2-Tf_2N-5-chloropyridine, –78 °C, 99%; m) $Pd(OAc)_2$, PPh_3, NBu_3, HCOOH, DMF, 40 °C, 89%; n) DIBALH, DCM, –78 °C, 88%; o) Na, NH_3, THF/EtOH, –78 °C, 100%; p) DOWEX 50WX2, THF/H_2O; q) Ag_2CO_3 on celite, toluene, 130 °C, 64% (two steps); r) DMDO, DCM, 96%; s) TsOH, DCM, 81%.

In this racemic synthesis of merrilactone A, Hirama et al. showcased an elegant stereocontrolled desymmetrisation reaction to generate the bicyclic core of merrilactone A, and at the same time, setting the relative stereochemistry of three stereocentres in a single reaction. Nevertheless, there are a number of selectivity difficulties affecting the synthesis at several stages, but even so, the total racemic synthesis of merrilactone A was accomplished in 27 steps with an overall 1% yield.

1.4.2.2 Asymmetric total synthesis

Building on their initial 2003 racemic synthesis, the Hirama group, reported in 2006 an asymmetric version of their total synthesis of merrilactone A. Investigations revealed the possibilty of using a bulky protecting group to induce long range stereo-controlling effects in the key intramolecular aldol reaction and in doing so, allowed access to the desired enantiomer out of the four possible isomers. This strategy required the use of an analogue of **57** (cf. Scheme 1-11), where both alcohols are differentially protected and consequently a new route was designed. The synthesis began with the reduction of 2,3-dimethylmaleic anhydride **20** followed by Wittig olefination and esterification to afford ester **63** in 68% yield over three steps (Scheme 1-13). Sharpless asymmetric dihydroxylation of **63** proceeded with excellent chemo- and enantioselective control and the resultant hydroxy-γ-lactone was protected as its pivaloate ester to give enantiomerically pure **64**. A [2+2] photocycloaddition of **64** with *cis*-1,2-dichloroethylene and the ensuing Zn-promoted eliminative dehalogenation furnished bicyclic **65**. In an effort to set-up the differential protecting group arrangement, **65** was reduced with LAH generating a 1,2-diol that was protected as its isopropylidene acetal **66** in 61% yield over two steps. The single primary alcohol is benzyl protected and acid-mediated cleavage of the acetonide provided monobenzyl-protected diol **67**. A one-carbon atom truncation of **67** to liberate the C14 primary alcohol was achieved via a two-step sequence in a one-pot reaction of $Pb(OAc)_4$-induced oxidative cleavage and DIBALH reduction. Next, followed a simple protection of the resulting primary alcohol as the *bis*-(trifluoromethyl)benzyl (BTB) ether affording the differentially protected **68**. A set of transformations previously demonstrated in the racemic synthesis (cf. Scheme 1-10) were used to convert from cyclobutene **68** to the intramolecular aldol substrate **69** in three steps.

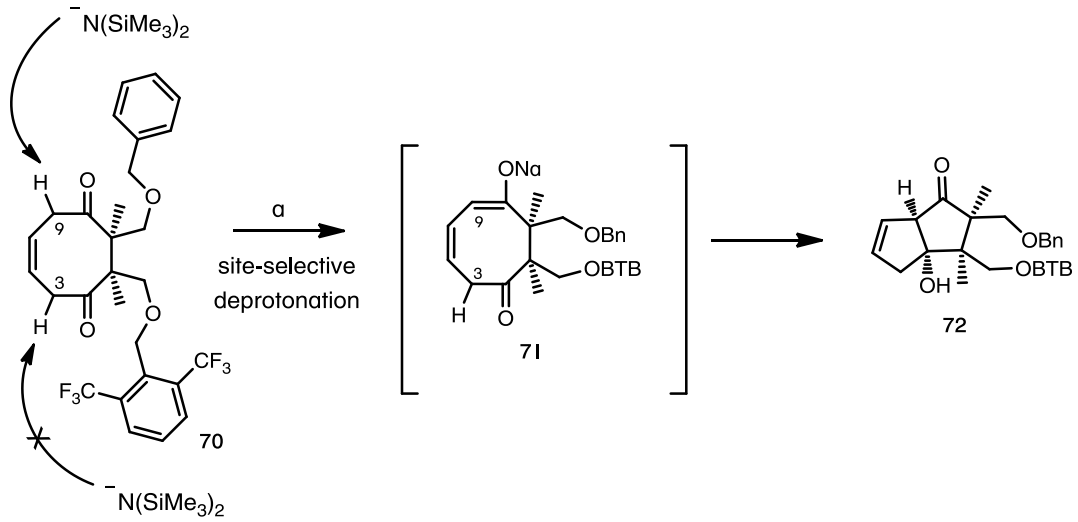
Scheme 1-13: Asymmetric synthesis of intramolecular aldol substrate **69**



a) $LiAlH(O^tBu)_3$, DME, –15 °C to RT, 85%; b) $Ph_3PCH_3^+Br^-$, ^{t}BuOK, 0 °C to RT, 87%; c) MeI, K_2CO_3, THF, 50 °C, 92%; d) AD-mix-α ^{t}BuOH/H_2O, 0 °C, 65%, >99% ee after recrystallisation; e) PivCl, pyridine, DMAP, DCM, 99%; f) *cis*-dichloroethylene, MeCN, -20 °C, hv; g) Zn, Ac_2O, toluene, 120 °C; h) $LiAlH_4$, Et_2O, 75% (three steps); i) $Me_2C(OMe)_2$, TsOH, DCM, 81%; j) BnBr, NaH, THF/DMF; k) 3M HCl, THF, 91% for 2 steps; l) $Pd(OAc)_4$, pyridine, DCM, –50 °C then DIBALH, –78 °C to –50 °C, 93%; m) BTBBr, KH, [18]crown-6, DMF; n) OsO_4, NMO, ^{t}BuOMe/^{t}BuOH/H_2O, 94% (two steps); o)SO_3·pyr, DIPEA, DMSO, DCM, –15 °C then allylmagnesium bromide, –78 °C, ratio α/ß 2.7:1, 78%; p) $[(PCy_3)_2Cl_2Ru{=}CHPh]$, TCM, reflux then $Pb(OAc)_4$, 97%.

The BTB protecting group developed by Hirama was used as a tool to enable site-selective deprotonation at C9 over C3 as a consequence of long-range steric interaction between the base and the trifluoromethyl substituents of the BTB group. The effect of the counter cation of the base was investigated revealing NaHMDS as the most selective. The desired bicyclo[3.3.0]octane **72** was furnished as the major enantiomer in 75% yield, with the remaining three possible diastereomers accounting for a further 22% yield (Scheme 1-14). This highly innovative diastereoselective transannular aldol reaction establishes the stereochemistry of four stereocentres in a single pot.

Scheme 1-14: Asymmetric synthesis of the core bicyclo-[3.3.0]octane framework



a) NaHMDS, THF, –100 °C, 97% overall, 75% **72**

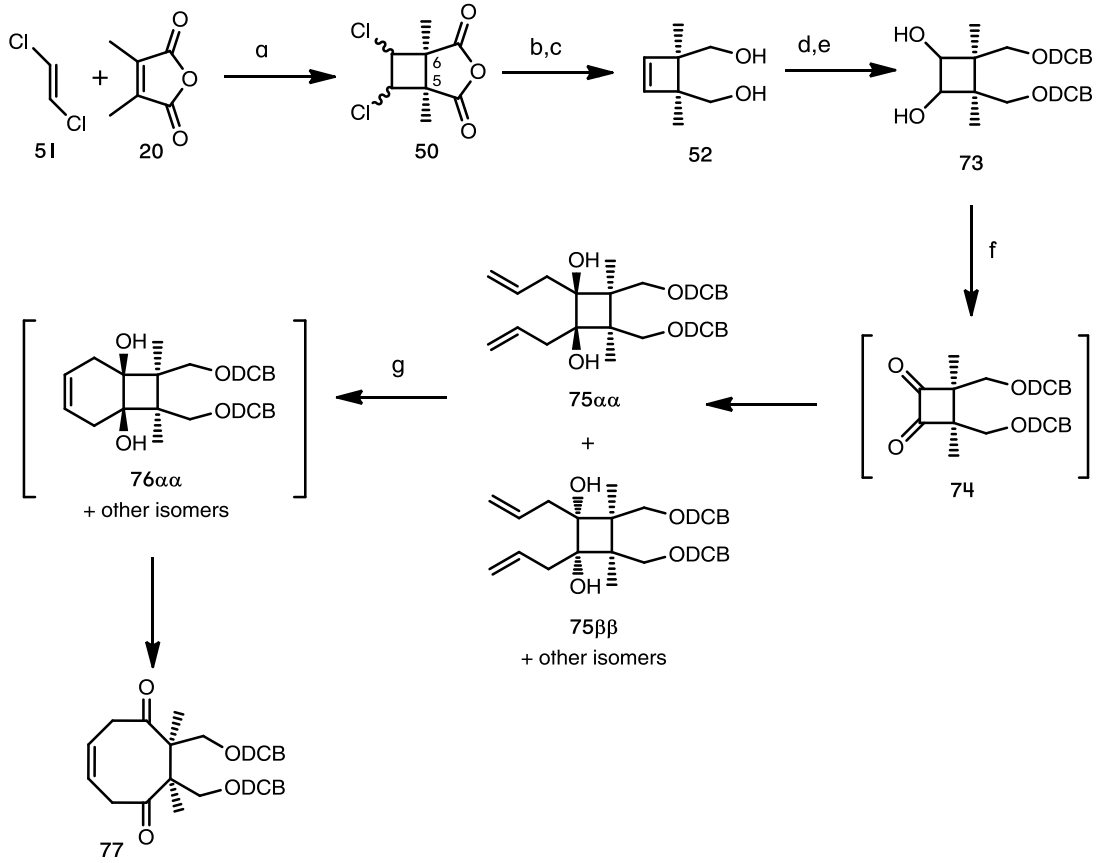
After reaching the milestone of enantiomer **72**, a facile conversion to (-)-merrilactone A was accomplished, by following a similar path to that previously established in the racemic synthesis (cf. Scheme 1-12). In this synthesis, the issue of selectivity of the transannular aldol reaction from the previous racemic synthesis was resolved by the use of a novel bulky protecting group as a long-range stereo-controlling element. This enabled access to key enantiomeric intermediate **72** under impressive regio- and stereoselective control. Enantiomer **72** was then converted to (-)-merrilactone A in a further 15 transformations, completing the total synthesis in a 1.1% overall yield over 31 steps.

1.4.2.3 Asymmetric total synthesis of ent-(+)-merrilactone A

Building on their previous elegant asymmetric synthesis of (-)-merrilactone A,[20] In 2007, Hirama and co-workers published a second asymmetric route to the unnatural (+)-enantiomer of merrilactone A.[21] In this synthesis, a strategy to replace the drawn-out sequence of differential protection of alcohols included the use of a chiral lithium amide base in the key transannular aldol reaction resulting in the selective deprotonation at C9 over C3. This allowed a more straightforward synthesis of the key aldol substrate as compared to the lengthy route in the asymmetric total synthesis of (-)-merrilactone A (cf. Scheme 1-13).

The synthesis begins with a photochemical [2+2] reaction between *trans*-dichloroethylene **51** and 2,3-dimethylmaleic anhydride **20**, followed by Zn-induced dehalogenation and LAH reduction, yielding diol **52** in a 57% yield over three steps (Scheme 1-15). In contrast to the previous asymmetric synthesis, both alcohols are protected as their respective 2,6-dichlorobenzyl (DCB) ethers, the protecting group found to impart the greatest selectivity in the key aldol reaction. A dihydroxylation furnished diol **73**, which was further elaborated via a one-pot Swern oxidation and double Grignard addition of allylmagnesium bromide to give predominantly diastereomer **75αα** over **75ββ** in a 9:1 ratio. The *cis*-arrangement of allyl groups facilitated the ring-closing metathesis to produce intermediate bicyclo-[4.2.0]octyl system **76αα**, which was treated with $Pb(OAc)_4$ *in situ* to yield the key *meso*-eight-membered diketone **77**.

Scheme 1-15: Synthesis of DCB protected *meso*-eight-membered diketone

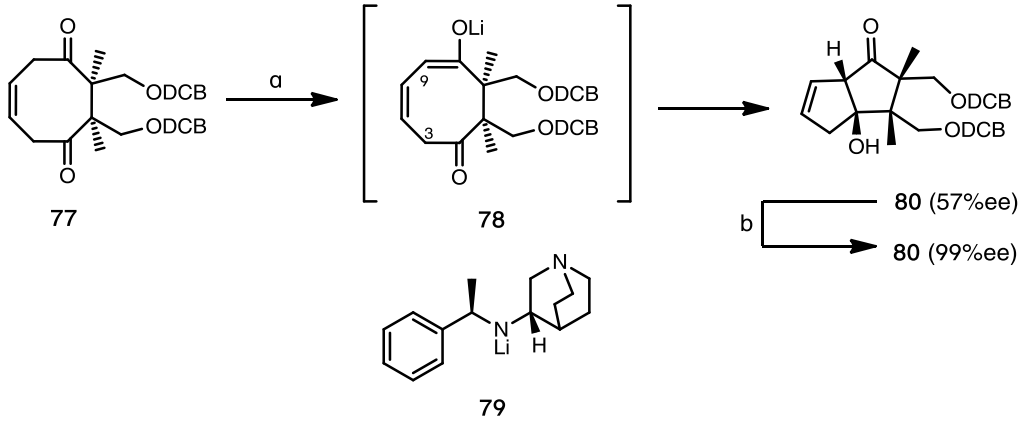


a) benzophenone, acetone, hv; b) Zn, TMSCl, Ac_2O, toluene, 85 °C; c) $LiAlH_4$, THF, 57% (three steps); d) DCBBr, NaH, THF/DMF; e) OsO_4, NMO, $^tBuOMe/^tBuOH/H_2O$, 91% (two steps); f) $(COCl)_2$, DMSO, NEt_3, DCM, –78 °C then allylmagnesium bromide, –78 °C, **75αα/75ββ** ratio 9:1, 80%; g) $(PCy_3)_2Cl_2Ru$=CHPh, DCM, reflux, then $Pb(OAc)_4$, 95%.

To accomplish the enantioselective transformation of *meso*-aldol substrate **77** into pure enantiomer **78** a variety of chiral amide bases were screened under the desymmetrisation reaction conditions. It was discovered that amine base **79** delivered the required selectivity over the other undesired enantio- and diastereomers, providing an enantioselective route to either enantiomer of merrilactone A. Exposure of **77** to chiral amine base **79** resulted in selective deprotonation at C9 over C3 providing lithium enolate **78** that underwent an intramolecular aldol reaction to afford enantioenriched **80** in 79% and 57% ee. A respectable 6:1 diastereomeric ratio was seen with a 4.7:1 enantiomeric ratio in

favour of the desired enantiomer **79**. The enantiopurity of **80** could be increased to 99% ee after a single recrystallization attempt in a 53% yield (Scheme 1-16).

Scheme 1-16: Enantioselective transannular aldol reaction using chiral base



a) **79**, LiCl, THF, –78 °C, 79%; b) recrystallisation, 1:1 EtOAc/hexane, 53%.

Utilising a chiral base in the transannular aldol reaction negated the need of a differential alcohol protection strategy, resulting in a more straightforward synthesis to enantiopure key intermediate **80**. This approach contained the added flexibility of accessing either enantiomer of merrilactone A by switching the chirality of the base. Enantiopure **80** was directed towards the total synthesis of *ent*-(+)-merrilactone A via conversions previously employed in both the racemic synthesis (cf. Scheme 1-12) and asymmetric synthesis variants. The total synthesis of the unnatural enantiomer of merrilactone A was accomplished in 23 steps with an overall yield of 1.3%. Investigations into the biological activity of the unnatural enantiomer unexpectedly revealed it to stimulate neurite outgrowth to a similar extent as the natural enantiomer. This represents one of the few instances where both enantiomers of a natural product or drug have similar levels of biological potency.[21]

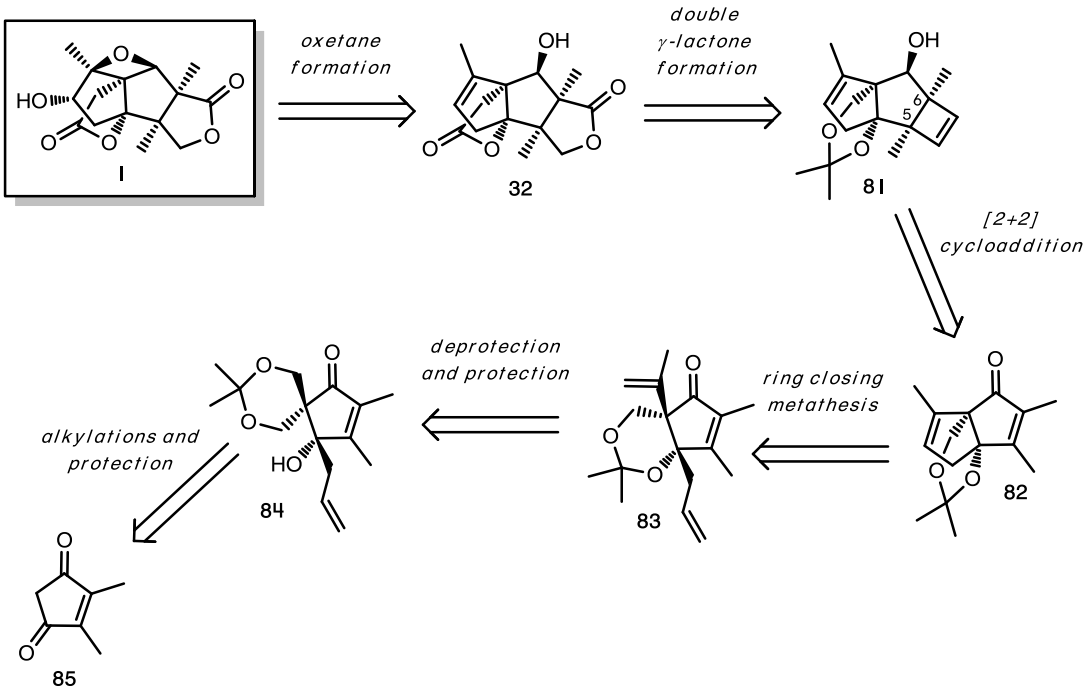
This final synthesis of merrilactone A by Hirama's group completes their efforts in developing their novel desymmetrisation strategy in the key intramolecular aldol reaction for the synthesis of merrilactone A. The use of chiral bases or a

protecting group strategy to generate enantioselectivity in the intramolecular aldol reaction provides an approach to both enantiomers of the natural product.

1.4.3 Mehta's racemic total synthesis

In 2005, Mehta and Singh published a novel synthetic route to the core of merrilactone A.[26] This research laid the groundwork for their racemic total synthesis of merrilactone A, which was reported in 2006.[22] Mehta's retrosynthetic approach to merrilactone A is outlined in Scheme 1-17.

Scheme 1-17: Mehta and Singh's retrosynthetic analysis of merrilactone A

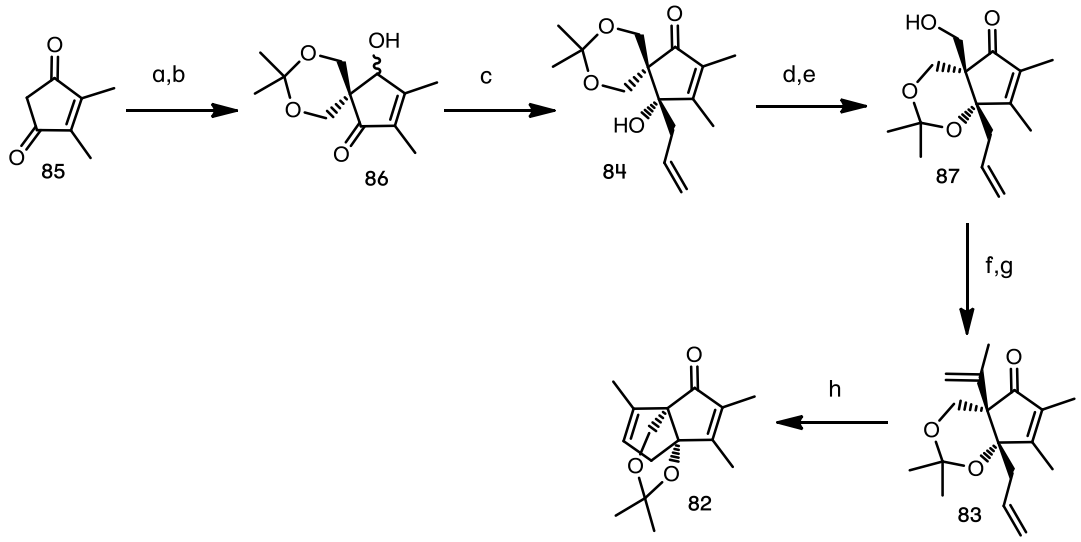


Analogous to previous syntheses of merrilactone A, the oxetane bridge would be installed by acid-induced *homo*-Payne rearrangement to provide racemic merrilactone A (**1**). *Bis*-lactone **32** was to be prepared from cyclobutene **81** by two γ-lactone syntheses, with one lactone originating from a hemi-acetal and the other through the ozonolysis of cyclobutene. Tetracycle **81** would be acquired from a [2+2] photocycloaddition reaction of tricycle **82**, establishing the contiguous C5 and C6 quaternary centres, and itself accessed through a crucial ring closing metathesis

reaction of diene **83**. A deprotection and protection sequence would give rise to diene **83** from acetonide **84**, identifying 1,4-dione **85** as a suitable starting point.[9]

The synthetic sequence began with the elaboration of 1,4-dione **85** that included a double hydroxylmethylation, subsequent acetonide protection and Luche reduction, furnishing **86** in 77% yield over three steps (Scheme 1-18). Combination of allylation followed by re-oxidation afforded hydroxyenone **84**, which itself was exposed to an acetonide deprotection-protection sequence. This sequence installed the four necessary side chains required for the on-coming RCM reaction and installation of the γ-lactone D ring. Thus, deprotection and re-protection of **84** under equilibrating conditions furnished a 1:1 mixture of **84** and **87**, which **84** was simply recycled to furnish **87** in 85% yield over two steps. PDC oxidation of the primary alcohol, methylation and a further oxidation, followed by a Wittig methylenation yielded RCM substrate **83** in 36% yield over four steps. The *cis*-orientated allyl- and propenyl-side-chains of **83** on exposure to Grubbs' first generation catalyst readily underwent the key ring closing metathesis reaction, affording tricycle **82** in a respectable 76% yield.[44]

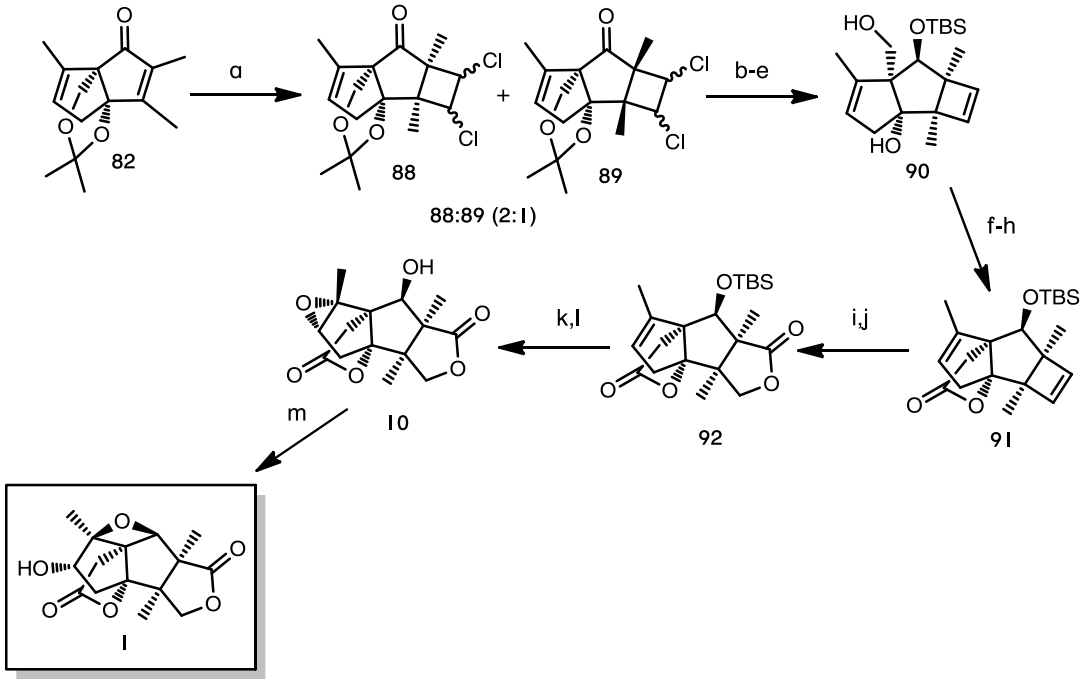
Scheme 1-18: Synthesis of RCM substrate and metathesis reaction



a) DBU, 40% HCHO, THF, 0 °C, 95%; b) acetone, MS, Amberlyst-15 then $NaBH_4$, $CeCl_3$, 0 °C, 83% (two steps); c) $CeCl_3$, allylmagnesium chloride, –78 °C, then MnO_2, DCM, 81%; d) 2M HCl, THF/H_2O, 90%; e) acetone, MS, amberlyst-15, 94%; f) PDC, DCM, then MeLi, Et_2O, 62% (two steps); g) PDC, DCM then Ph_3PCH_3Br, ^tBuOK, Et_2O, 58% (two steps); h) Grubbs' catalyst I, DCM, reflux, 76%.

Photochemical [2+2] cycloaddition of *trans*-1,2-dichloroethylene and tricycle **82** proceeded only with a moderate degree of β-facial selectivity, directed by the steric bulk of the acetonide methyl groups positioned on the α-face, to deliver a readily separable mixture of isomers, **88** and **89** in a 2:1 ratio, in a combined yield of 65% (Scheme 1-19). Eliminative dichlorination, DIBALH reduction, TBS protection of the resulting alcohol and acetonide deprotection, furnished the diol **90** in 54% yield over four steps. TPAP oxidation of **90**, furnished an intermediate aldehyde, which was homologated via a Wittig methoxymethylenation to give an enol ether, followed by acid-mediated hydrolysis and subsequent PCC oxidation afforded γ-lactone **91** in four steps. Elaboration of the cyclobutene ring began with exposing **91** to ozone to yield a di-aldehyde intermediate, which was reduced *in situ* with sodium borohydride and oxidised to deliver *bis*-γ-lactone **92**. The total synthesis was straightforwardly accomplished via well-known transformations that included TBS deprotection and an acid-induced *homo*-Payne rearrangement to complete the synthesis of merrilactone A (**1**).

Scheme 1-19: Final transformations from key tricyclic intermediate **82** to merrilactone A



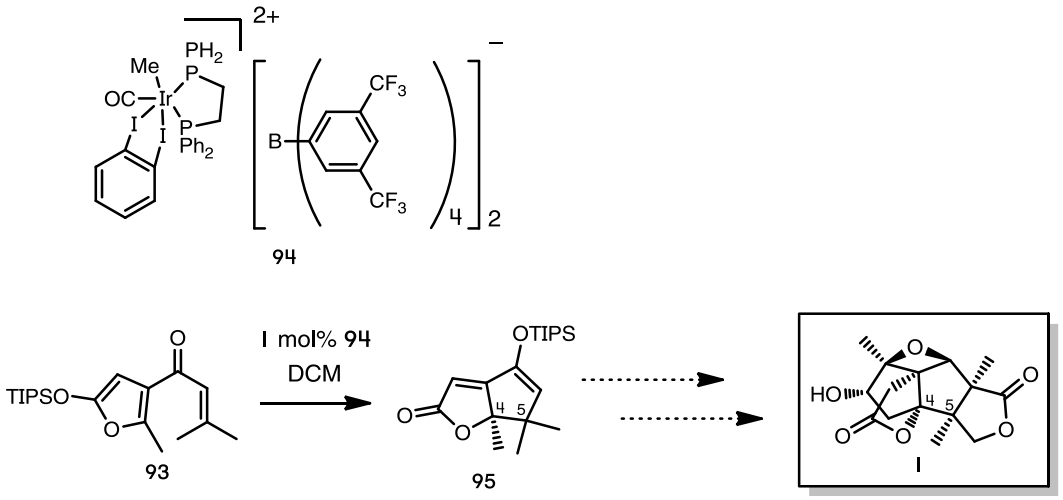
a) *trans*-dichloroethylene, hv, **88:89** (2:1), 65%; b) sodium naphthalenide, –60 °C, 70%; c) DIBALH, –78 °C, 95%; d) TBSOTf, NEt_3, DCM, 86%; e) 2M HCl, THF/H_2O, 95%; f) TPAP, DCM then $Ph_3PCH_3OCH_3$, ^tBuOK, THF, 54% (two steps); g) $HClO_4$, DCM/THF; h) PCC, DCM, 62% (two steps); i) O_3, MeOH, –78 °C then $NaBH_4$, MeOH, –78 °C, 45%; j) PCC, DCM, 80%; k) TBAF, AcOH, THF, 85%; l) DMDO, 95%; m) TsOH, DCM, 80%.

To conclude, Mehta and Singh have provided a route to racemic merrilactone A in 27 steps with an overall yield of 0.4%. Examination of the synthetic route highlights the possibility of an asymmetric variant, but nevertheless, other areas of concern would initially have to be addressed, most notably the poor selectivity observed in the [2+2] photocycloaddition.

1.4.4 Frontier's racemic total synthesis

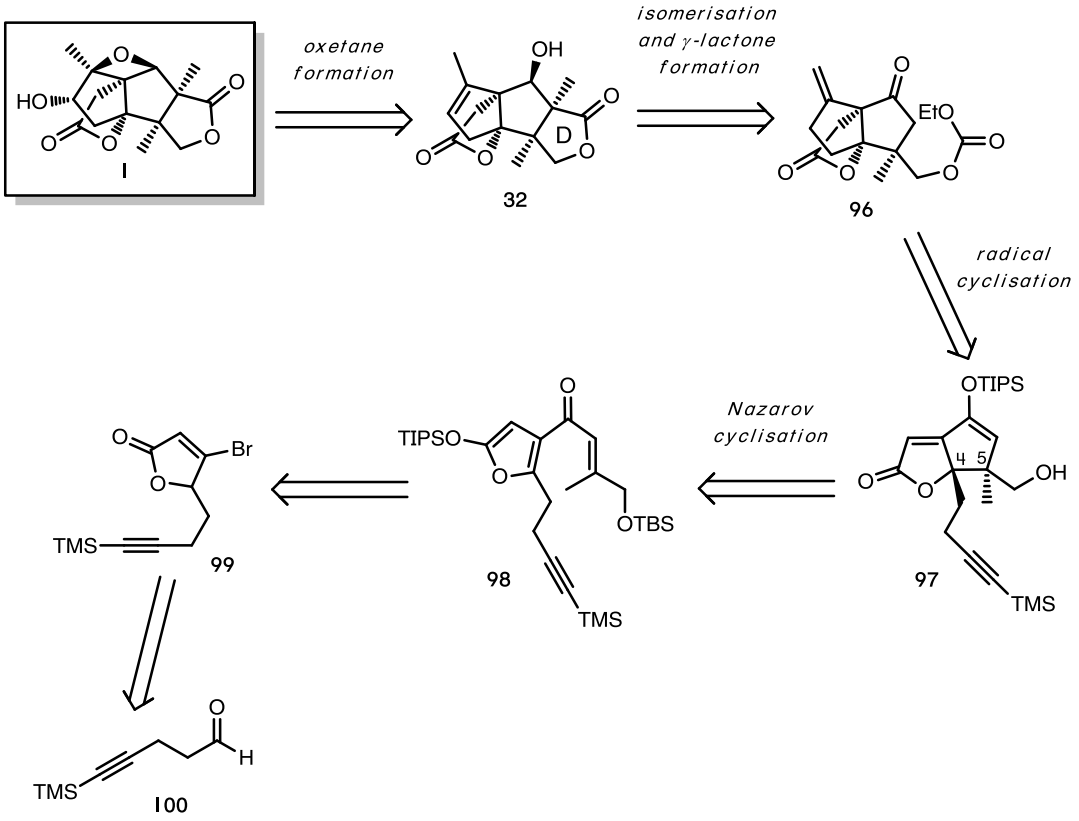
Frontier and co-workers have developed the Nazarov cyclization of polarised divinyl ketones in the hope of incorporating this methodology in the total synthesis of (±)-merrilactone A.[45-47] They successfully incorporated the Ir-catalysed Nazarov reaction of a silyloxyfuryl enone **93** in the presence of 1 mol % of **94** to assemble the oxabicyclo[3.3.0]octane skeleton **95** of merrilactone A.[24] In this proposed strategy, they intended to simultaneously introduce the C4 and C5 quaternary centres through the implementation of the catalytic Nazarov cyclisation (Scheme 1-20).

Scheme 1-20: Catalytic Nazarov key cyclisation reaction



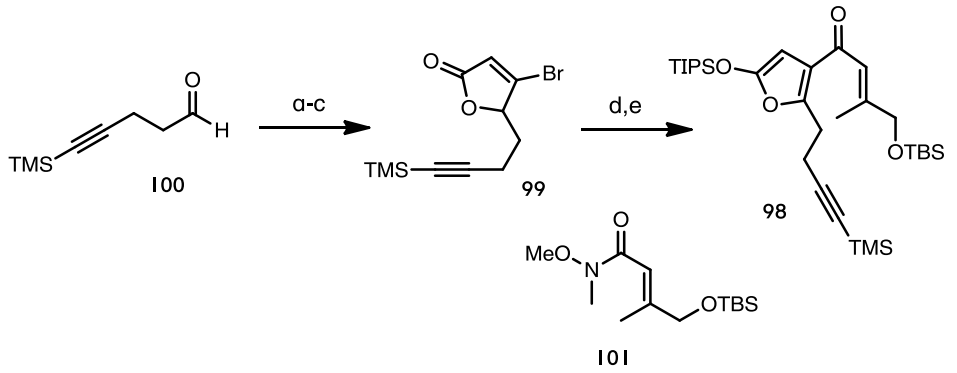
Frontier reported their total synthesis in 2007[23] and followed this with a full account of their efforts in 2008.[24] Their retrosynthetic strategy first relied upon the well-known combination of epoxidation and *homo*-Payne rearrangement to convert **32** to merrilactone A (**1**) (Scheme 1-21). Tetracycle **32** is derived from *exo*-olefin **96** via acid-induced double bond isomerisation and a late-stage lactonisation, installing the γ-lactone D-ring. Subsequently, **96** would be generated by the means of a radical cyclisation approach from bicycle **97**, which in turn, is accessed via the critical Nazarov cyclisation reaction of substrate **98**. Examination of the Nazarov cyclisation substrate identified **99** as a precursor that could easily be prepared from the readily available aldehyde **100**.

Scheme 1-21: Frontier's retrosynthetic analysis of merrilactone A



The approach to the key Nazarov cyclisation substrate began with the organometallic 1,2-addition of lithiated ethyl propiolate to known aldehyde **100**. The ensuing diyne in the presence of a higher order stannyl cuprate underwent a lactonisation delivering a vinyltin compound and a subsequent tin bromide exchange delivered vinyl bromide **99**. The key Nazarov substrate **98** was obtained by treating **99** with triisopropylsilyl triflate followed by lithiated addition to α,β-unsaturated Weinreb amide **101** (Scheme 1-22).

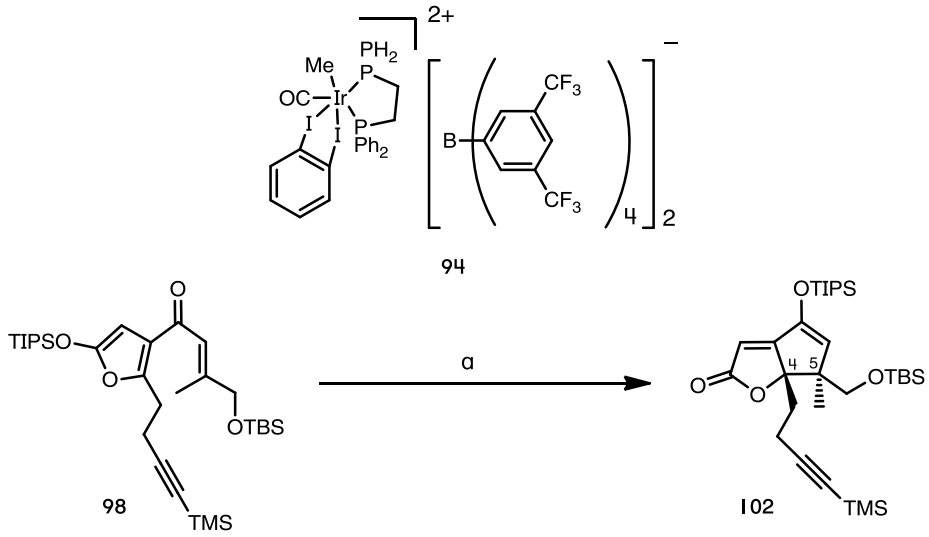
Scheme 1-22: Synthesis of key Nazarov cyclisation substrate



a) ethyl propiolate, ^{n}BuLi, THF, –78 °C, 88%; b) $Bu_3Sn(Bu)(CN)CuLi_2$, THF/MeOH, –78 °C, 90%; c) Br_2, DCM, 93%; d) NEt_3, TIPSOTf, DCM, –78 °C to 0 °C, quant.; e) ^{t}BuLi, Et_2O, then **101**, 82%.

This sets the stage for the important Nazarov cyclisation, which was executed by exposing silyloxyfuran **98** to 2 mol% of dicationic iridium catalyst **94**, yielding a single diastereomer of the bicycle **102**. During this transformation, the desired stereochemistries at C4 and C5 are introduced in a stereospecific manner due to the conrotatory nature of the 4π electrocyclic pathway of the Nazarov cyclisation (Scheme 1-23).

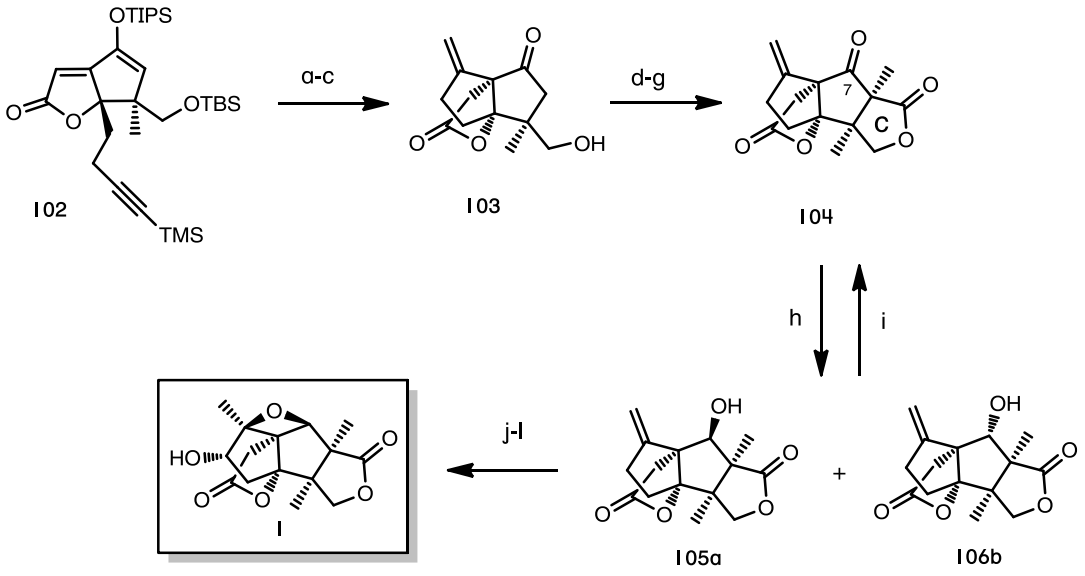
Scheme 1-23: Catalytic Nazarov cyclisation silyloxyfuran **98**



a) **94** (2 mol%), DCM, 87%.

Removal of the trimethylsilyl group of **102** afforded the substrate for the radical cyclisation reaction. Subsequent exposure to tributyl tinhydride, followed by TBAF global deprotection conditions, *exo*-methylene **103** was obtained in 65% yield over four steps. The late-stage installation of the γ-lactone D-ring followed a four-step sequence of converting the primary alcohol to a carbonate, intramolecular nucleophilic lactonisation and α-methylation, to deliver *bis*-lactone **104**. The main carbon framework of merrilactone A is now complete with only a stereoselective carbonyl reduction at C7 required to access an intermediate that has previously been transformed by Danishefsky to merrilactone A. Unfortunately, the facial selectivity of the reduction was poor, yielding a mixture of **105a** and **106b** in a ratio of 1.2:1, respectively. The undesired isomer **106b** was recycled via a Dess-Martin oxidation to fully convert all material to the desired isomer **105a.** In accordance with previous total syntheses, the *exo*-olefin was isomerised under acidic conditions to give a known intermediate that in two steps via epoxidation and a *homo*-Payne rearrangement yielded racemic merrilactone A.

Scheme 1-24: Final stages of the synthesis of (±)-merrilactone A



a) $AgNO_3$, KCN, THF/EtOH/H_2O, 83%; b) AIBN, Bu_3SnH, PhH, reflux then TsOH, 91%; c) TBAF, THF, 99%; d) pyridine, DMAP, ethylchloroformate, 95%; e) NaH, THF; f) TsOH, PhH, reflux, 90% (two steps); g) NaH, MeI, HMPA, THF, 97%; h) $NaBH_4$, MeOH, d.r. **105a**:**106b** (1.2:1), 93%; i) **106b**, DMP, DCM, 98%; j) TsOH, PhH, reflux, 92%; k) *m*CPBA, DCM, l) TsOH, DCM, 68% (two steps).

In completing the total synthesis of merilactone A, Frontier demonstrated the utility of a novel iridium-catalysed Nazarov cyclisation in the construction of fused carbocycles and in natural product synthesis. Even more impressive, is the fact this was achieved in a remarkable 17 steps with a highly impressive overall yield of 19%, making this the most efficient synthesis of racemic merilactone A to date.

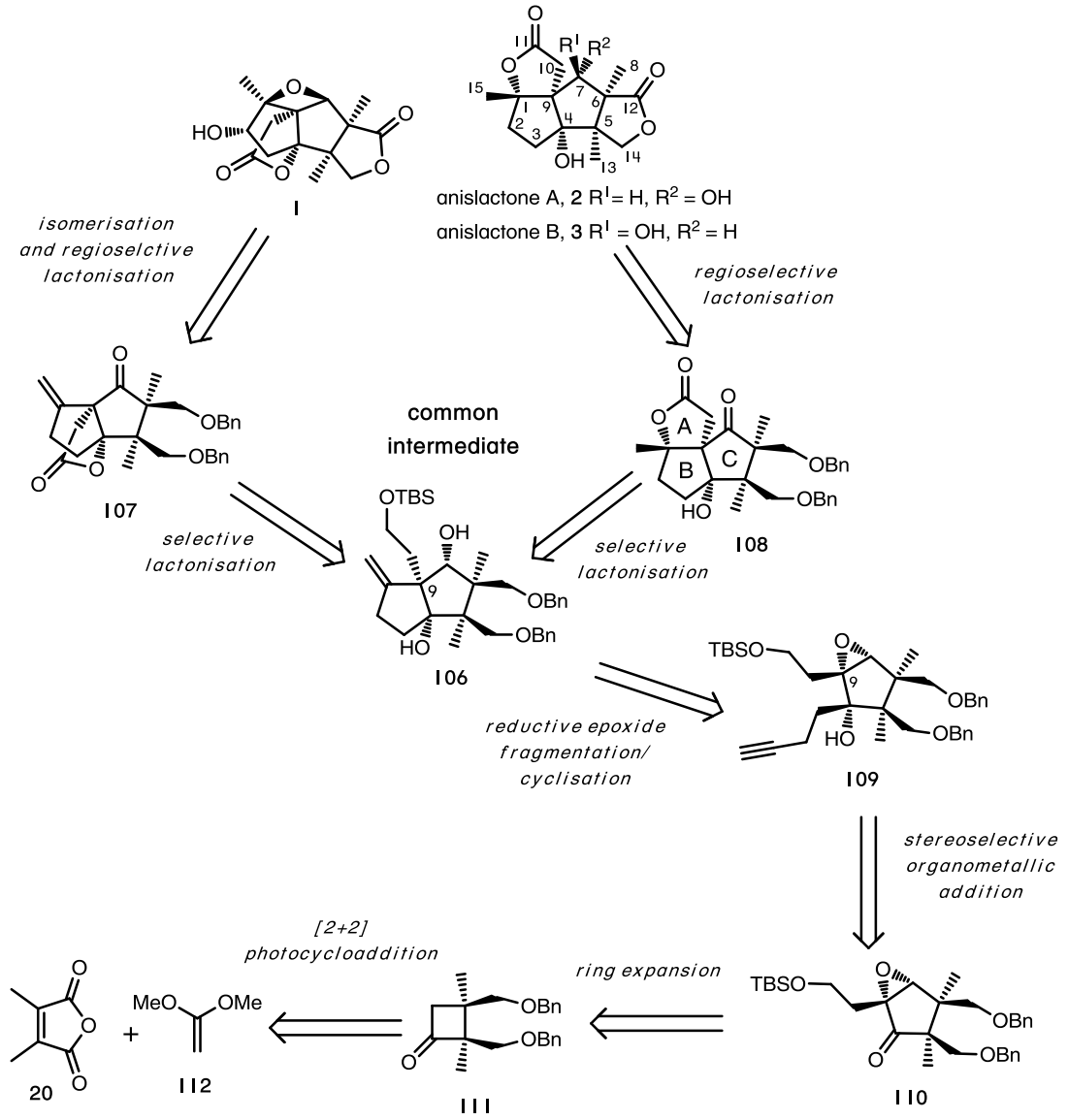
1.4.5 Greaney's syntheses of Merrilactone A and Anislactone A

In 2005, the Greaney group reported a radically different approach to merrilactone A. In all previous syntheses of the natural product, the oxetane bridge was installed in the final step via an effective *homo*-Payne type rearrangement. The Greaney group instead proposed a [2+2] Paternò-Büchi photo-addition to facilitate the introduction of this key structural motif. The development of this approach proved ultimately unsuccessful, but did lay the foundation for a successful synthesis via alternative chemistry.[28] As recently as 2010, the Greaney group published a formal racemic synthesis of merrilactone A and the first total synthesis of closely related anislactone A via a common intermediate.[25] The defining transformation in their synthesis is a reductive epoxide cleavage-cyclisation that establishes the stereochemistry of the C9 quaternary stereocentre.

The retrosynthetic approach highlights a strategy to access the core tricyclic structures of both anislactones A/B and merrilactone A via a selective lactonisation of common intermediate **106** (Scheme 1-25). Starting with merrilactone A (**1**), the central oxetane motif would be again constructed from the well-established procedures of *homo*-Payne rearrangement, selective epoxidation and isomerisation of the *exo*-alkene. A regioselective Fetizon oxidation was anticipated to install the γ-lactone D-ring of tricycle **107**, a procedure adapted from Hirama's total synthesis of merrilactone A.[19] Common intermediate **106** would be directed to **107** or the tricyclic ABC core **108** of anislactone A via selective formation of the γ-lactone A-ring. The total synthesis of anislactone A (**2**) was expected to proceed from

tricycle **108** via a series of oxidations and reductions including the aforementioned regioselective Fetizon oxidation. An obvious milestone in this synthesis will be the preparation of common intermediate **106** that would be accessed from highly functionalised **109** via an ambitious reductive epoxide cleavage-cyclisation, installing the highly congested C9 stereocentre. Tertiary alcohol **109** was believed to be accessible through a stereoselective organometallic addition of ketone **110**, which in turn could be prepared by a regioselective ring-expansion of a cyclobutane derivative **111**. The latter was suggestive of a [2+2] photocycloaddition between commercially available dimethylmaleic anhydride **20** and dimethylketene acetal **112**.

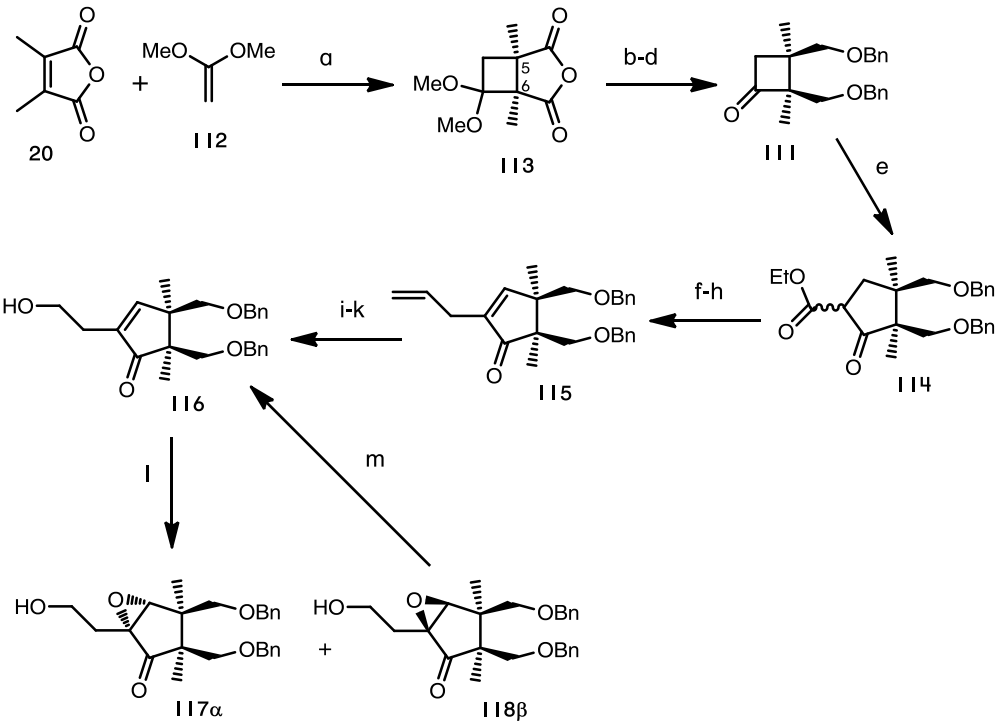
Scheme 1-25: Retrosynthetic analysis of merrilactone A (**1**) and anislactones A/B (**2**/**3**)



The synthesis began with [2+2] photocycloaddition of 4,5-dimethylmaleic anhydride **20** and dimethylketene acetal **112**, affording cyclobutane **113** with the requisite *cis*-methyl groups at newly formed quaternary centres C5 and C6 (Scheme 1-26). Subsequent LAH reduction, benzyl protection and ketal hydrolysis, produced cyclobutanone **111**, the substrate for a regioselective ring expansion, in 87% yield over three steps. A Tiffeneau-Demjanov type reaction, using ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$, converted cyclobutanone **111** to the required cyclopentanone. With the C-ring now formed, transesterification of **114** with allyl

alcohol and C-alkylation of the formed ß-keto ester, furnished the substrate for a Tsuji-Trost decarboxylation-dehydrogenation reaction. Treatment with catalytic $Pd(OAc)_2$ and PPh_3 afforded cyclopentenone **115** in 70% over three steps. Oxidative cleavage of the terminal alkene followed immediately by a chemoselective $ZnBH_4$ reduction of the resultant aldehyde furnished cyclopentenone **116**. The desired α-epoxide was prepared via NaOCl treatment of enone **116** in excellent yield but only moderate diastereoselectivity, yielding a separable diastereomeric mixture of **117α:118β** in a 2.2:1 ratio. The unwanted ß-epoxide was recycled through reductive deoxygenation using $[Cp_2TiCl_2]$ to improve the efficiency of the transformation.

Scheme 1-26: Synthesis of highly functionalised cyclopentenone C-ring **117α**

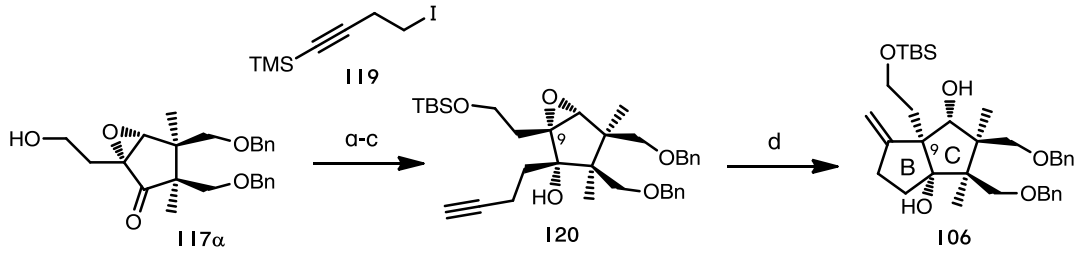


a) *hv*, pyrex, MeCN/acetone (9:1), 96%; b) $LiAlH_4$, Et_2O, 0 °C, 97%; c) BnBr, TBAI, NaH, THF; d) H_2SO_4 (aq), MeCN, 90% (two steps); e) N_2CHCO_2Et, $BF_3{\cdot}Et_2O$, DCM, 0 °C, 88%; f) allyl alcohol, toluene, reflux, 93%; g) allyl bromide, K_2CO_3, acetone, 89%; h) $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), MeCN, reflux, 90%; i) OsO_4 (2 mol%), NMO, acetone/H_2O (4:1), 96%; j) $NaIO_4$,THF/H_2O (1:1); k) $ZnBH_4$·pyridine, isopropyl alcohol, 0 °C, 76% (two steps); l) NaOCl (aq), pyridine, 0 °C, 90%, d.r. **117α:118ß** (2.2:1); m) $[TiCp_2Cl_2]$ (2 equiv), Zn (6 equiv), THF, 70%.

A TBS alcohol protection of **117α** led to a diastereoselective organometallic addition of lithiated homopropargyl reagent **119** to an extremely hindered ketone affording a

single diastereomer, which after desilylation presented substrate **120** for the key reductive epoxide fragmentation/cyclisation reaction (Scheme 1-27). Treatment of **120** with [$TiCp_2Cl_2$] and zinc resulted in reductive cleavage of the epoxide followed instantly by a 5-*exo*-dig cyclisation onto the pendant alkyne. In this transformation, the sterically challenged C9 stereocentre is installed resulting in BC bicycle **106**, which contains the full carbon skeleton of both merrilactone and anislactone, enabling a regiodivergent approach to both natural products.

Scheme 1-27: Construction of BC core via a key reductive epoxide cleavage cyclisation



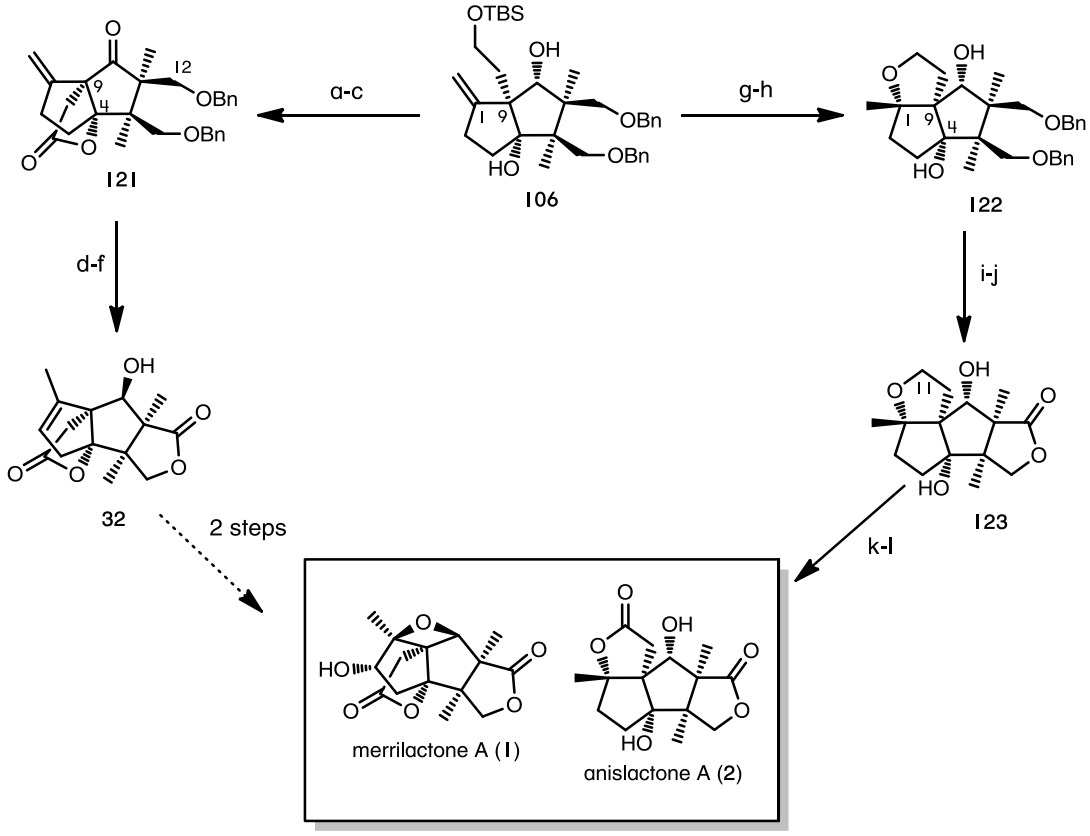
a) TBSCl, imidazole, DCM, 0 °C, 98%; b) **119**, ^tBuLi, Et_2O, –78 °C, 94%; c) KOH, MeOH, 98%; d) [Cp_2TiCl_2], Zn, THF, 69%, 10% starting material recovered.

The conversion to merrilactone A from common intermediate **106** started with TPAP oxidation, TBAF desilylation and oxidative lactonisation to afford tricyclic compound **121** (Scheme 1-28). Careful treatment of **121** with a TsOH/AcOH mixture delivered the internal alkene in high yield. Application of Hirama's two-step procedure of global debenzylation and regioselective Fetizon oxidation,[20] provided tetracycle **32** in 22% yield over three steps. Tetracycle **32** has been demonstrated in all previous syntheses to be easily directed towards merrilactone A, by the well-established two-step protocol of epoxidation followed by acid-induced *homo*-Payne rearrangement. Thus, a formal synthesis of racemic merrilactone A was achieved in an overall yield of 2.4% over 22 steps (24 steps to the natural product).

Anislactone A was too accessed from common intermediate **106** by installing the other regioisomeric lactone between C1 and C9, as compared to C4 and C9 in merrilactone A. Accordingly, TBAF-mediated desilylation and treatment with a catalytic amount of $Al(OTf)_3$ resulted in tricycle **122**. Once again, a global

debenzylation followed by regioselective Fetizon oxidation led to tetracycle **123**. Subsequent oxidation at C11 of the cyclic ether resulted in simultaneous oxidation of the secondary alcohol to ketone. Reduction of the ketone yielded anislactone A and B in 95% yield, as a 5:1 mixture from which anislactone A (**2**) was isolated completing the synthesis. This represents the first total synthesis of anislactone A, which was completed in 22 steps with an overall yield of 5.7%.

Scheme 1-28: Final transformations to merrilactone A (**1**) and anislactone A (**2**)



a) TPAP (0.5 equiv), NMO, MS. 4Å, DCM, 82%; b) TBAF, THF; c) TPAP (0.1 equiv), NMO, M.S. 4Å, DCM, 90% (two steps); d) TsOH, AcOH/DCM (1:1), 30 °C, 78% (5% starting material recovered); e) Na, liq NH_3, THF/EtOH (5:1), –78 °C; f) Ag_2CO_3 on celite, toluene, 130 °C, 28% (two steps); g) TBAF, DCM/THF (5:1); h) $Al(OTf)_3$ (5 mol%), DCM, 88% (two steps); i) H_2, Pd/C, MeOH; j) Ag_2CO_3 on celite, toluene, 130 °C, 73% (two steps); k) $RuCl_3$ (0.5 equiv), $NaIO_4$, $MeCN/CCl_4/H_2O$ (1:1:1), 73%; l) $NaBH_4$, THF, 95% d.r. 5:1.

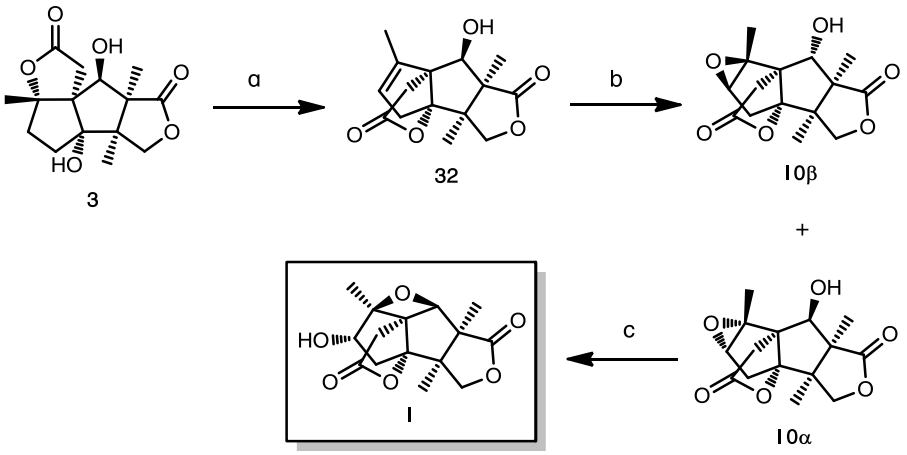
In summary, Greaney and co-workers have presented an approach to both merrilactone A and anislactone A via a common route. At the heart of the synthesis

is the reductive epoxide cleavage-cyclisation reaction, which allows access to both natural products via a shared intermediate.

1.5 Fukuyama's Chemical Conversion of Anislactone B to Merrilactone A

Fukuyama and colleagues previously reported in 2000 the isolation of merrilactone A from *Illicium merrillianum*[11] and further studies in 2001 revealed additional anislactone-type sesquiterpene constituents including relatively large quantities of anislactone B.[12] It was shown that merrilactone A could be synthesised from anislactone B in three relatively simple steps. The synthesis began with treating anislactone B (**3**) with trifluoroacetic acid under refluxing conditions that resulted in the formation of γ-lactone at C4 and dehydration of the C1 hydroxyl gave tetracycle **32** in a 92% yield (Scheme 1-29). Next, a stereoselective epoxidation of **32** furnished a separable mixture of the desired α-epoxide **10α** and unwanted β-epoxide **10β** in 64% and 4% yield, respectively. The peroxyacid attacked predominantly from the less hindered convex face of **32** giving rise to a highly stereoselective epoxidation. The oxetane ring was constructed in the last step by exposing **10α** with *p*-toluenesulfonic acid, which resulted in a *homo*-Payne type rearrangement affording merrilactone A, in 78% yield. Common to all subsequent total syntheses of merrilactone A is this acid-induced *homo*-Payne rearrangement as a feasible method of installing the oxetane bridge in the final synthetic step of this natural product.

Scheme 1-29: Chemical conversion of anislactone B (**3**) to merrilactone A (**1**)



a) TFA, reflux, 90%; b) *m*CPBA, DCM, **10α:10β** (64%:4%); c) *p*TsOH, DCM, 78%.

1.6 Published Approaches towards Merrilactone A

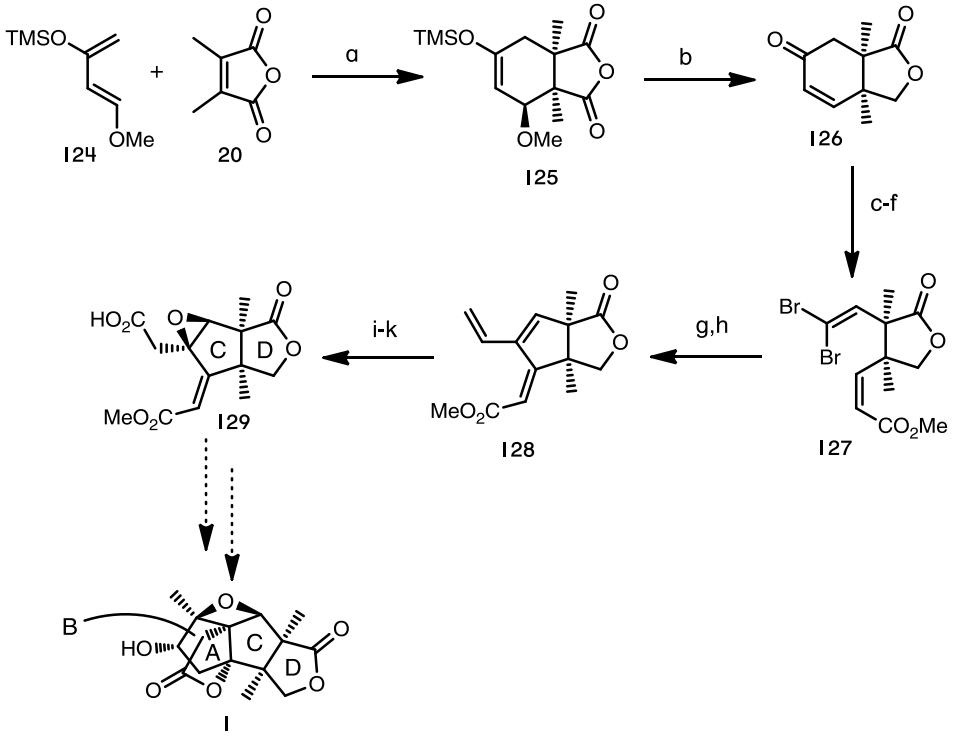
1.6.1 Fukuyama's model studies 1+2

Back in 2000, Fukuyama's group was the first to isolate merrilactone A from *Illicium merrillianum*, and in that research uncovered its intriguing biological activity.[11] This early research was responsible for much of the subsequent generated research interest in anislactone-type sesquiterpenes, culminating in several total syntheses of merrilactone A. Fukuyama's group has also shown their own desire to complete a total synthesis of the natural product and have published two model studies; a synthesis of the CD ring motif was reported in 2005[27] and in 2007 an approach for the synthesis of the AB ring system was disclosed.[29]

Fukuyama's group strategy to the CD ring system of merrilactone A is presented in Scheme 1-30. The synthesis began with a Diels-Alder addition of Danishefsky's diene **124** and dimethylmaleic anhydride **20**, furnishing bicycle **125**, which was regioselectively reduced using Super-Hydride ($Li(C_2H_5)_3BH$), affording enone **126**. Treating **126** with $Pb(OAc)_4$ followed by an acid-hydrolysis gave an α-hydroxyketone, which underwent oxidative cleavage upon treatment with further $Pb(OAc)_4$ and the ensuing aldehyde was converted to dibromoalkene **127** via the

Corey-Fuchs procedure. Both bromides were then used in a stepwise, palladium catalysed coupling sequence consisting of a successive Stille and Heck coupling, affording the bicyclic system **128** in 48% yield. Since both reactions utilise Pd(0) as the active catalytic species, the feasibility of one-pot procedure was investigated. Diluting the first Stille coupling with DMF and adding two equivalents of triethylamine to initiate the Heck reaction successfully furnished bicycle **128** in one-pot with a slightly improved yield of 52%. Further elaboration of **128** via hydroboration, PDC oxidation and *m*CPBA epoxidation, afforded the tricycle **129**. Fukuyama's model study accomplished the synthesis of the densely functionalised intermediate **129** containing the required CD ring system of the natural product in a total yield of 1.6% over 11 steps.

Scheme 1-30: Fukuyama's model study of CD ring system

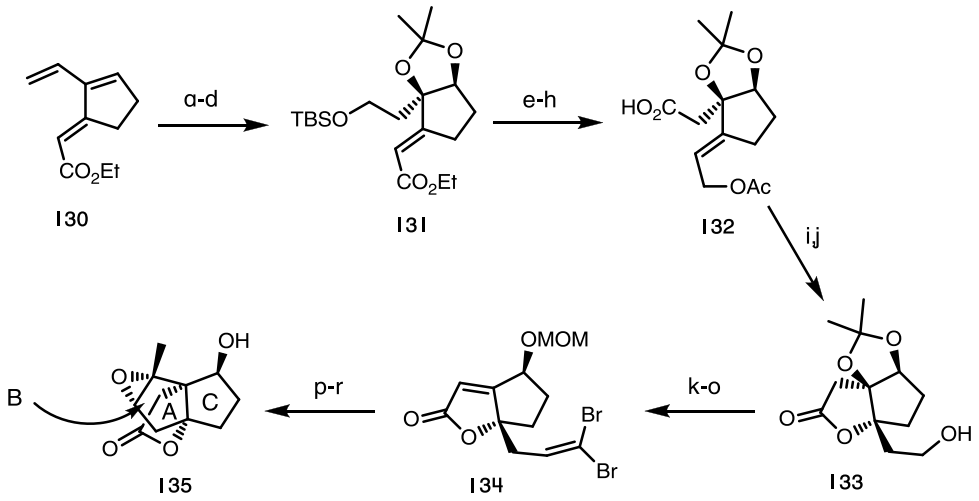


a) Toluene, 150 °C, 63%; b) $Li(C_2H_5)BH$, THF, 74%; c) $Pb(OAc)_4$, PhH, reflux, 87%; d) TsOH, $MeOH/H_2O$, 100 °C, 72%; e) $Pb(OAc)_4$, PhH, MeOH, 76%; f) CBr_4, PPh_3, DCM, 74%; g) vinyltributyltin, $Pd_2(dba)_3$-CH_3CN 10 mol%, trifurylphosphine 20 mol%, toluene, 100 °C, 62%; h) $Pd(OAc)_2$ 20 mol%, P(*o*-tol)$_3$, NEt_3, DMF, 100 °C, 78%; i) Sia_2-BH, Et_2O, H_2O_2, 73%; j) PDC, DMF, 62%; k) *m*CPBA, DCM, 44%.

The second model study focuses on a synthetic pathway to the ABC ring system of merrilactone A. The synthesis started with hydroboration of triene **130**, representing the C-ring, followed by TBS protection of the resulting primary alcohol. A regioselective dihydroxylation and protection of the resulting diol then furnished acetonide **131** (Scheme 1-31). A series of four transformations that included DIBALH reduction, acetylation, desilylation and PDC oxidation, then supplied the substrate **132** for the Tsuji–Trost reaction. The critical Tsuji–Trost reaction of **132** and subsequent hydroboration of the resultant alkene gave rise to the desired γ-lactone **133**. In a similar fashion to the first model study, the substrate **134** for the Stille-Heck coupling sequence was obtained from **133** via oxidation, a Corey-Fuchs reaction, acetal hydrolysis, MOM alcohol protection and elimination of the tertiary alcohol. Unfortunately, exposure of **134** to the previously optimised conditions of the Stille-Heck coupling sequence yielded no desired product with only unreacted starting material remaining. Optimisation led to the discovery of dimethyllithium cuprate as an effective reagent for the desired regioselective *mono*-methylation of the *trans*-Br and subsequent Michael-type cyclisation to the conjugated lactone moiety. Finally, a MOM deprotection followed by stereospecific *m*CPBA epoxidation furnished epoxide **135**, encompassing the ABC ring system of merrilactone A. This second model study by Fukuyama has demonstrated the applicability of this synthetic route in accessing the ABC core **135** of merrilactone A in 18 steps and 1.2% combined yield.

In these two model studies, Fukuyama and co-workers, have demonstrated the ability to construct both sides of the merrilactone A carbon skeleton in a relatively efficient manner. Research to combine these two approaches in an effort towards a total synthesis of the natural product is reportedly ongoing.

Scheme 1-31: Fukuyama's model study of the ABC ring system



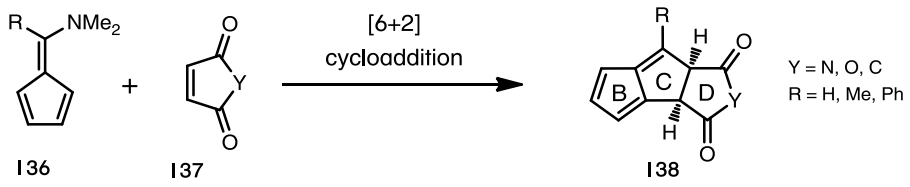
a) $(Sia)_2BH$, THF then aq. NaOH, H_2O_2, 88%; b) TBSCl, imidazole, DMF, 95%; c) OsO_4 3 mol%, NMO, THF; d) 2,2-dimethoxypropane, TsOH, DCM, 56% (two steps); e) DIBALH, DCM; f) Ac_2O, DMAP, pyridine, 89% (two steps); g) TBAF, THF; h) PDC, DMF, 67% (two steps); i) $Pd(PPh_3)_4$, NaH, DMF, 75%; j) BH_3-THF complex, THF then aq. NaOH, H_2O_2, 58%; k) DMP, DCM, quant; l) CBr_4, PPh_3, DCM, 64%; m) 1M HCL, THF, 71%; n) MOMCl, DIPEA, DCM, 76%; o) MsCl, NEt_3, DCM, 67%; p) Me_2CuLi, Et_2O, 78%; q) DOWEX 500WX2-100, MeOH, 88%; r) *m*CPBA, DCM, 66%.

1.7 Published Approaches to Anislactones A/B

1.7.1 Hong's model study towards Anislactones A/B

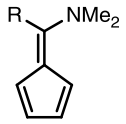
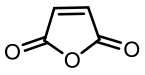
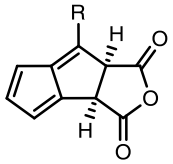
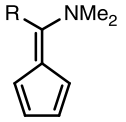
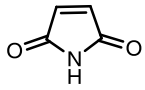
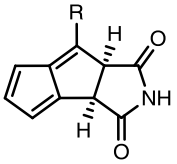
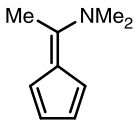
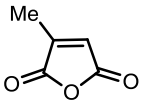
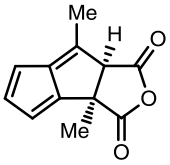
The epimeric anislactones A (**2**) and B (**3**) have received very little synthetic attention with only one reported total synthesis in 2010 by the Greaney group.[25] The only other report was by Hong *et al.* in 2002 on an approach to the tricyclic BCD core of the anislactone framework.[48] In this model study by Hong and co-workers, a novel one-pot [6+2] cycloaddition reaction of fulvenes **136** with alkenes **137** was shown to be an effective route to the BCD core of the anislactones (Scheme 1-32).

Scheme 1-32: [6+2] cycloaddition of fulvenes with alkenes to the anislactone BCD core



A few examples of reactions between homologous maleic anhydride and maleimide, with various aminofulvenes are outlined in Table 1-1. Reaction of various aminofulvenes with maleic anhydride or maleimide in benzene at room temperature, furnished the desired tricycle products **139-145** in good yields. In this single transformation, three rings are formed and the stereochemistry of two stereocentres is established. In entry 3, reaction of a substituted maleic anhydride with dimethylaminofulvene under microwave irradiation gave tricycle **145** with one of the two required *cis*-methyl groups installed.

Table 1-1: Scope of the reaction of fulvenes and alkenes

entry	fulvene	alkene	product		method	yield (%)
1				**139** R = Me **140** R = Ph **141**/**125** R = H	A A A	81 73 70
2				**142** R = Me **143** R = Ph **144** R = H	A A A	81 73 70
3				**145**	B	63

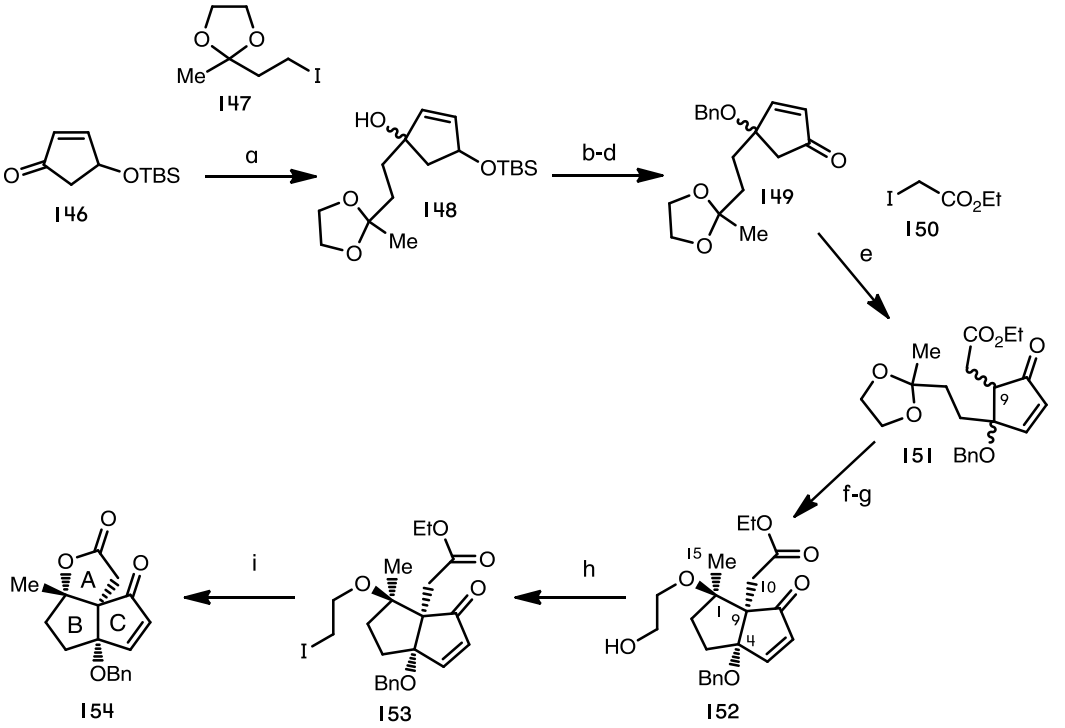
Method A: PhH, 25 °C; **Method B:** microwave irradiation at 10W in DMF, 120 °C.

In summary, Hong and colleagues have demonstrated the applicability of a novel one-pot [6+2] cycloaddition of fulvenes to alkenes to access structurally complex tricycles constituting the BCD core of the anislactones. Extending this methodology to the synthesis of various natural products is reportedly being investigated.

1.8 Greaney's Unpublished Model Study Towards Anislactones A and B

Synthesis of anislactone-type sesquiterpenes are a current research focus within the Greaney group, and previous work by Jesus Perea-Buceta revealed a nine-step route to the ABC core of anislactones A and B (Scheme 1-33).[49]

Scheme 1-33: Greaney and co-workers' model study to the ABC core of anislactones A/B



a) **147**, ^{t}BuLi, Et_2O, –78 °C, 85%, d.r. 8.5:1 *(cis:trans);* b) BnBr, TBAI, NaH, THF, 70 °C; c) TBAF, THF; d) PDC, DCM, 74% (three steps); e) **150**, ^{t}BuLi, THF, –78 °C, 78%, d.r. 2:1 *(cis:trans);* f) NEt_3/TMSCl, LiHMDS, THF, –78 °C; g) $TiCl_4$, DCM, –78 °C, 47% (two steps); h) I_2, PPh_3, imidazole, PhH, 86%; i) Zn dust, MeOH, 73%.

Leading off with an organometallic nucleophilic addition using lithiated iodo-dioxolane **147** to the TBS protected hydroxycyclopentenone **146**, yielded tertiary alcohol **148** as a 8.5:1 (*cis:trans*) mixture of diastereomers in 85% yield. Benzylation of **148** followed immediately by desilylation and PDC oxidation, furnished the alkylated cyclopentenone **149** in 74% yield over three steps. Alkylation of cyclopentenone **149** suffered from irreproducibility due to enol-lactone formation under the reaction conditions, but still yielded **151** as a 2:1 mixture of diastereomers in 78% overall yield. Enone **151** served as the substrate for an extremely hindered

Mukaiyama acetal-aldol reaction that installed the triad of neighbouring fully-substituted stereocentres at C1, C9 and C4. The yield of this reaction is a meager 47%, and is unfortunately highly selective for the R-configuration at C1 of **152**. Confirmation was obtained by NOESY analysis revealing signal enhancements between the methylene protons at C10 and the C15 methyl group. This is in agreement with the structural assignments and suggests that the reaction proceeds via a chelated transition state in favour of the undesired stereochemistry at C1. Conversion of the alcohol **152** to the ethyl iodide **153** and ensuing zinc-mediated dealkylation resulted in the clean inversion of stereochemistry at C1 delivering the required ABC core **154** in 63% yield over two steps. It was proposed that the tertiary alcohol undergoes a retro-aldol/aldol equilibration under the zinc-based reductive cleavage conditions, which is a known phenomenon in the anislactone family of natural products.[13] Under these equilibrating conditions, any α-alkoxide produced will immediately lactonise to **154**, providing a thermodynamic driving force for the transformation. This model study identified two key challenges for successful synthesis of anislactones A/B:

- the alkylation of C9 and the Mukaiyama aldol reaction suffer from irreproducibility and mediocre yield, respectively; and
- there is insufficient functionality present in the C-ring to enable completion of the synthesis.

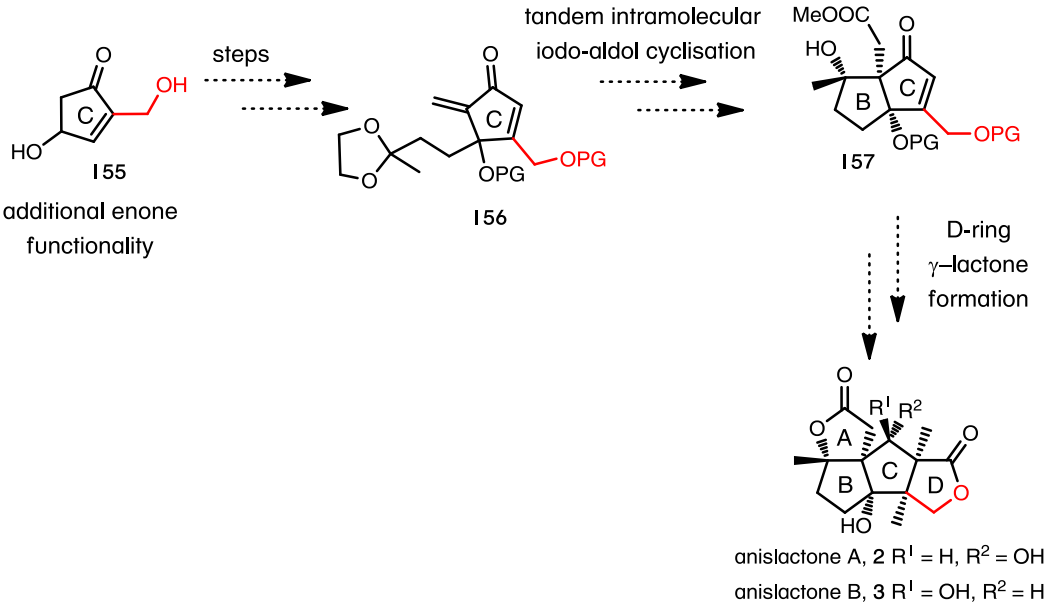
In this model study, Greaney and coworkers have successfully demonstrated a novel approach to the construction of the ABC core of the anislactones A/B via nine synthetic steps in an overall yield of 14%. This research laid the foundation for future work towards a total synthesis of anislactones A/B.

2 Synthesis of the Bicyclic Core of Anislactones A/B

2.1 Tandem Iodo-Aldol Intramolecular Cyclisation Approach

In this approach we plan to address the challenges raised in the methodology previously developed within this project as discussed in Section 1.8. We envisage adding the necessary functionality in the C-ring early on in the synthesis and replacing the poor alkylation of C9 and Mukaiyama aldol reactions with a novel tandem iodo-aldol intramolecular cyclisation reaction (Scheme 2-1). Iodo-aldol cyclisation reactions are a current research interest of the Greaney group and this would be a highly appropriate test of that methodology in the natural product arena.

Scheme 2-1: Proposed solutions to challenges identified in a previous model study

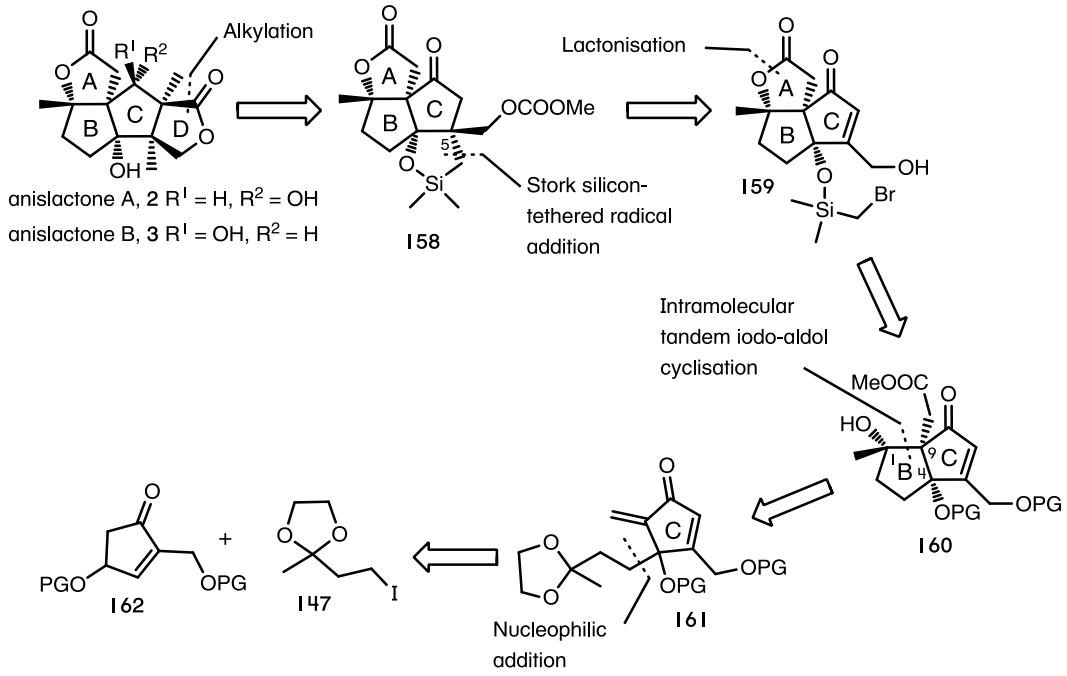


2.2 Retrosynthetic Analysis

The proposed retrosynthetic analysis for anislactones A/B reveals four key transformations (Scheme 2-2). Our proposed strategy for the total synthesis of **2** and **3**, utilises a late stage alkylation that installs the final γ-lactone D-ring. Next, we aim to carry out a stereospecific Stork silicon-tethered radical addition to enone **159**

giving rise to **158**.[50] The intramolecularity of the reaction, allied to the relatively low sensitivity of radical additions to steric hindrance, will ensure successful addition to what would otherwise be a very hindered Michael acceptor in the intermolecular variant. Following this critical formation of the C5 quaternary stereocentre, enone **159** would in turn be prepared by an established deprotection/lactonisation sequence (cf. Scheme 1-33). The defining step in our synthesis is the construction of the bicyclic BC core via an intramolecular tandem iodo-aldol cyclisation reaction. This one-pot reaction forms a five-membered ring and simultaneously sets the stereochemistry of three fully substituted stereocentres at C1, C9 and C4. Iodo-aldol substrate **161** is anticipated to be available from a stereocontrolled nucleophilic addition to cyclopentenone **162**, a known compound easily accessed from precedented furan-cyclopentenone rearrangement chemistry and an appropriate starting point for the synthesis.[51]

Scheme 2-2: Retrosynthesis of anislactones A/B **2**/**3** including key transformations

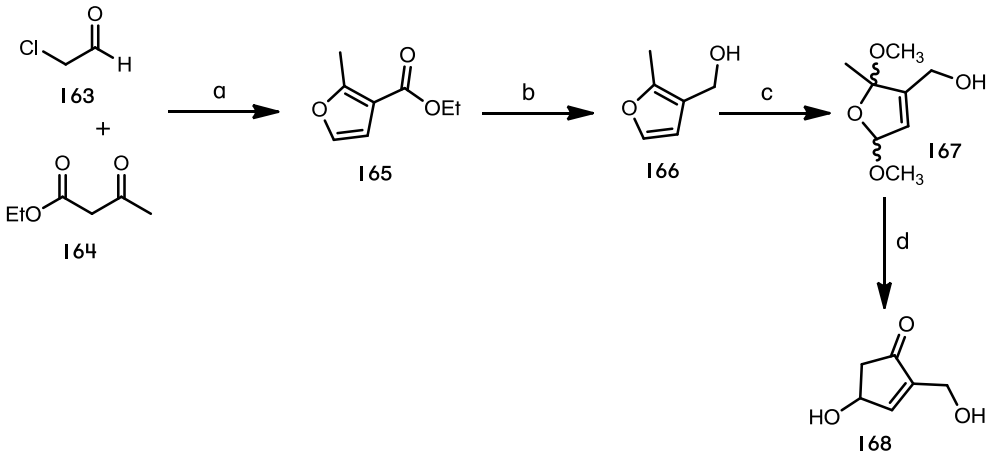


2.3 Synthesis of the Bicyclic BC Core of Anislactones A/B

2.3.1 Synthesis of cyclopentenone-diol starting material

Our first challenge in implementing our synthetic strategy towards anislactones A/B lay in accessing hydroxymethylated cyclopentenol **168**, a literature compound easily accessed from precedented furan-cyclopentenone rearrangement chemistry by Stoodely and co-workers.[51] Reaction of commerically available chloroacetaldehyde **163** and ethyl acetoacetate **164**, led to furan ester **165** in excellent yield (Scheme 2-3). This step was amenable to efficient scale-up, and after distillation, delivered large quantities of the desired **165**. A lithium aluminium hydride reduction of the ethyl ester in **165** and subsequent treatment with bromine in methanol gave dihydrofuran **167** as an inseparable 2:1 mixture of diastereomers. Rearrangement of **167** to racemic cyclopentenone **168** was achieved by refluxing **167** in aqueous dioxane buffered to pH 6.3 with a catalytic amount of hydroquinone. After an intramolecular aldol reaction of a 1,4-diketone intermediate, this afforded **168** in 50% yield over four steps.[52,53]

Scheme 2-3: Synthesis of hydroxymethylated cyclopentenol **152**

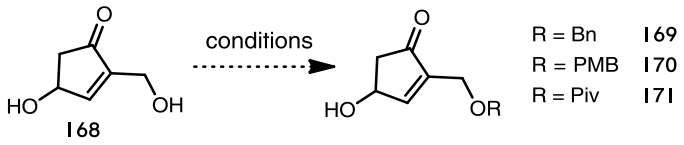


a) Pyridine, RT, 94%; b) $LiAlH_4$, Et_2O, 0 °C, 91%; c) Br_2, NEt_3, MeOH:Et_2O (4:1), –78 °C, 89%; d) hydroquinone, 1,4-dioxane, 0.2 M potassium phosphate buffer, reflux, 71%.

2.3.2 Regioselective protection of the 1° allylic alcohol

Having prepared cyclopentenone **168**, a regioselective protection of the primary allylic alcohol in the presence of a secondary alcohol was required. As both alcohols will ultimately be differentially protected, it was vital to select protecting groups that are orthogonal under deprotection conditions. The possibility of a benzyl protecting group was investigated but this proved to be unsuccessful as significant amount of decomposition was observed by TLC. We suspected the substrate may be unstable under the basic reaction conditions and subsequent treatment alone, with a variety of bases such as sodium hydride, sodium methoxide and DBU, resulted in the same decomposition. The high density of reactive sites in the ring, the acidic proton in the γ-position and the two acidic δ-protons, are perhaps jointly responsible for the observed decomposition. Other protecting groups were explored under a variety of conditions, and in the event of there being no decomposition, unreacted starting material remained with a mixture of *mono*- and *bis*-protected products (Figure 2-1). Introduction of a benzyl group under acidic conditions using benzyl trichloroacetimidate[54,55] and the formation of a pivalate ester, which is reportedly selective for primary alcohols, proved to be both ineffective.[56]

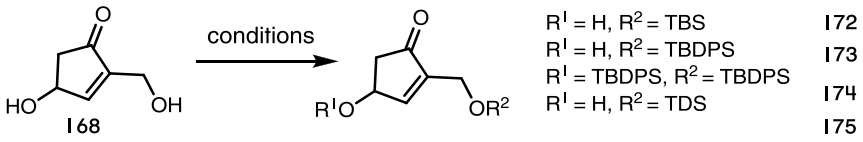
Figure 2-1: A table summarising the various types of protecting groups and conditions investigated for the regioselective protection of the primary allylic alcohol



Product	Conditions	Result
169	BnX (X= Cl, Br), TBAI, NaH or NaOMe, DCM, DMF or THF, RT to 100 °C	Decomposition
169	BnX (X= Cl, Br), TBAI, DIPEA, proton sponge, RT to 130°C	SM and mixture of products
169	Benzyl trichloroacetimidate, PPTS, DMF or THF, RT to 100 °C	SM and decomposition
170	PMBCl, TBAI, NaH or NaOMe, DCM, DMF or THF, RT to 100 °C	Decomposition
170	PMBCl, TBAI, DIPEA, Proton sponge, RT to 130 °C	SM and mixture of products
171	PivCl, pyridine, RT	SM and mixture of products

Our attention then focussed on the prospect of using hindered silicon-based protecting groups because of their ease of formation under neutral conditions, removal and stability to a variety of reagents and conditions.[57,58] A range of bulky silyl-protecting reagents were screened, anticipating that the added steric bulk would result in an effective discrimination between the 1° and 2° allylic alcohols (Figure 2-2).

Figure 2-2: Examples of silyl protecting agents used in the regioselective protection of **168**



Entry	Conditions	Yield (%)	Result
1	TBSCl, DMF, imidazole, DMAP, RT	41	**172**[a] and *bis*-protected byproduct
2	TBSOTf, DMF, 2,6-lutidine, –45°C	45	**172**[b] and *bis*-protected byproduct
3	TBDPSCl, DMF, imidazole, DMAP, RT	40	**173**[a] and **174** (23% yield)
4	TDSCl, DMF, imidazole, DMAP, RT	41	**175** and *bis*-protected byproduct

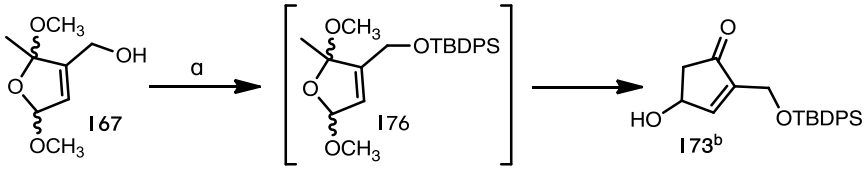
[a] Method A was used in the synthesis; [b] Method B was used in the synthesis

We were pleased to successfully obtain the desired *mono*-protected primary alcohol with no decomposition using a range of chloro variants of silyl protecting groups but only in moderate yields (entries 1,3 and 4). It was hoped that thexyldimethylsilyl (TDS) chloride would be more selective as has been demonstrated in the literature.[59,60] However, TDS protected **175** was obtained with no improvement as compared to TBS **172** and TBDPS **173** ethers. Attempts to increase the selectivity by decreasing reaction temperature proved unsuccessful as the reaction became too sluggish and only unreacted starting material remained. It was hoped that using the more reactive *tert*-butyldimethylsilyl (TBS) triflate at –78 °C (entry 2) will discriminate between the different reactivities of the allylic alcohols, but this only gave a slight improvement in yield. The major byproduct in all cases was the formation of the *bis*-protected alcohol, such as TBDPS *bis*-protected **174** which was isolated in 23% yield. This posed problems during scale-up, although **174** was

formed in low yield, its molecular weight is almost double that of the desired *mono*-protected which caused difficulties during large scale-up.

An alternative approach was to preemptively protect the hydroxyl group in furan **167** before the furan-cyclopentenone rearrangement, thereby directly accessing *mono*-protected **173**, avoiding the regioselective protection and purification issues (Scheme 2-4).

Scheme 2-4: Pre-emptive protection of primary allylic alcohol for the synthesis of **173**



a) i) TBDPSCl, imidazole, DMAP, DMF, RT; ii) hydroquinone, DMF, potassium phosphate buffer, reflux, 30% (two steps). [b] **Method B** was used in the synthesis.

TBDPS ether formation of **167** under standard conditions went as expected and afforded the crude **176**. This was sufficiently pure to be used in the next step; the furan rearrangement to the cyclopentenone. Unfortunately, the now less polar dihydrofuran **176** did not rearrange easily due to insolubility in the aqueous buffer. The additional steric bulk of the TBDPS group likely contributed to the ineffectiveness of the rearrangement. Consequently, the reaction was much slower and did not go to completion even after refluxing for 48 hr. A number of different solvent combinations were screened and a DMF:phosphate buffer (2:1) mixture delivered the best results. However, the reaction was slow, taking 24 hr to reach completion and afforded **173** in a mediocre 30% yield over the two steps. As this offered no improvement, our efforts then focused on advancing through the synthesis taking advantage of the enhanced stability of TBDPS ether **173** obtained from diol **168** despite the aforementioned regioselectivity and purification problems.

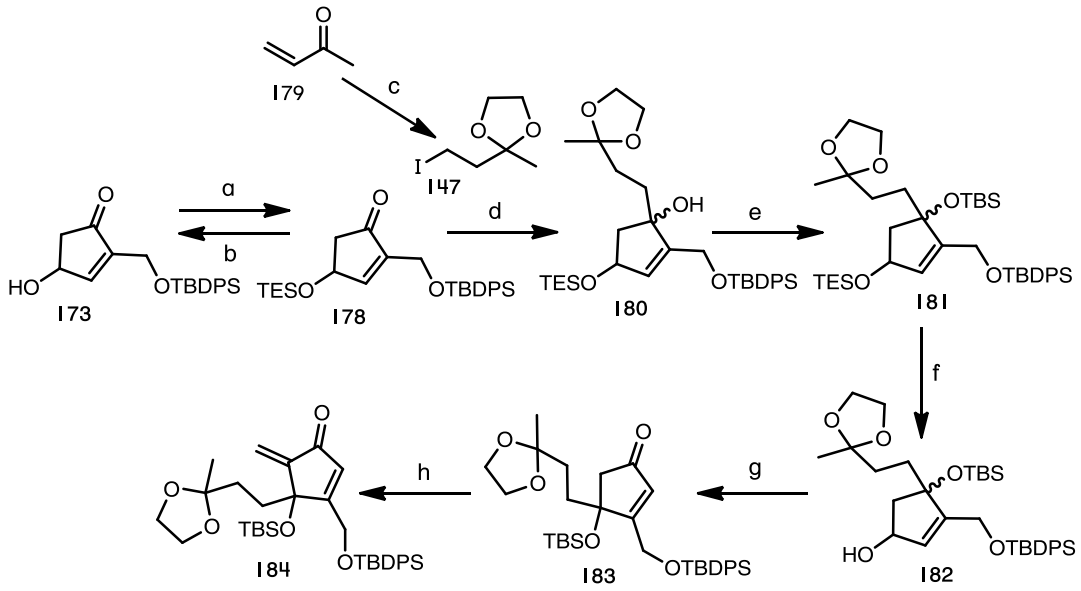
2.3.3 Synthesis of iodo-aldol cyclisation substrate

We proceeded towards the key iodo-aldol cyclisation reaction with the synthesis of the iodo-aldol substrate as our first target. A 1,1-disubstituted alkene like **184** would be necessary for the key cyclisation. This was anticipated to successfully undergo the tandem conjugate iodo-aldol cyclisation to furnish the desired BC bicyclic core **199** (Scheme 2-5). An initial large-scale preparation of **173** provided sufficient multi-gram quantities to be carried forward through the synthesis. Subsequent protection of the secondary alcohol as the TES ether gave diprotected cyclopentenone **178** (Scheme 2-5). A key feature of silyl protecting groups is their different stabilities towards deprotection conditions, such as DDQ, protic acids and fluoride ion sources.[58] The TES protecting group in the presence of DDQ is substantially less stable than more sterically hindered groups such as TBS or TBDPS ethers.[61] This was investigated and treatment of enone **178** with 0.1 equiv DDQ cleanly deprotected the TES alcohol leaving the TBDPS group untouched and afforded alcohol **173** in a very good 80% yield.

Next, the iodoacetal **147** was prepared from methyl vinyl ketone **179** in a one-pot reaction with trimethylsilyl chloride, sodium iodide and ethylene glycol in acetonitrile.[62] The scene was now set for the key organolithium addition between the prepared iodoacetal **147** and cyclopentenone **178**. Treatment of **147** with *tert*-butyllithium in Et_2O at –78 °C initiated the lithium-iodide exchange forming the organometallic nucleophile, which was transferred slowly to cyclopentenone **178** resulting in the clean formation of tertiary alcohol **180** as a single diastereomer. The TES group at stereocentre C7 controlled the facial selectivity of the organolithium addition, efficiently transferring stereochemistry to C4. However, this has little importance as the C4 stereocentre will be destroyed later in a separate deprotection and oxidation sequence.

Subsequently, the TBS protection of the sterically hindered tertiary alcohol using the highly reactive TBSOTf furnished cyclopentene **181** in almost quantitative yield. A concern for the next reaction was the stability of the dioxolane and TBS ether moieties to the previously demonstrated catalytic DDQ-mediated TES-deprotection conditions. As anticipated, a mixture of products was obtained when **181** was treated with DDQ, resulting in both TES ether and ketal deprotection. Tanemura and co-workers reported significant reactivity differences of various silyl ethers and acetals to DDQ and other π-acceptors.[63] Switching to the enhanced chemoselectivity of TCNQ, TES deprotected alcohol **182** was obtained in excellent yield with the other protecting groups left intact. Subsequent DMP oxidation afforded enone **183**, which was treated with LDA followed by Eschenmoser's salt and successive elimination of the formed dimethylaminoethylene Mannich base product with *m*CPBA. This successfully delivered the desired *exo*-methylene **184** in 67% yield over two steps and meant we had now achieved our first milestone.

Scheme 2-5: Synthesis of the substrate for the key iodo-aldol cyclisation reaction



a) TESCl, NEt_3, DMAP, DCM, reflux, 96%; b) **Method C**: DDQ, MeCN:H_2O (9:1), RT, 80%; c) NaI, TMSCl, $HO(CH_2)_2OH$, MeCN, 49%; d) **147**, ^{t}BuLi, Et_2O, –78 °C to RT, 83%; e) TBSOTf, 2,6-Lutidine, DMF, RT, 99%; f) TCNQ, THF:H_2O (9:1), RT, 88%; g) DMP, DCM, RT, 95%; h) i) LDA, $[CH_2{=}NMe_2]^+ I^-$, THF, –78 °C; ii) *m*CPBA, DCM:$NaHCO_3$ (2:1), RT, 67% (two steps).

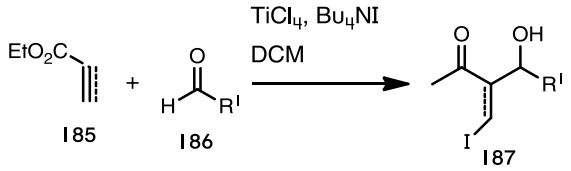
The synthesis of the substrate for the key intramolecular tandem iodo-aldol cyclisation reaction had been accomplished in 12 synthetic steps with an overall yield of 10%. At this stage it was apparent that the preparation of the desired substrate was for the most part straightforward. However, the regioselective *mono*-protection of either allylic alcohol in cyclopentenone-diol **168** was inefficient and the poor regioselectivity, together with purification problems during scale-up, provided an opportunity for future improvement.

2.3.4 Intramolecular iodo-aldol cyclisation reaction

The iodo-aldol reaction is part of the Morita-Baylis-Hillman (MBH) family of tandem conjugate addition/aldol processes and has become a well-developed strategy for C–C bond formation.[64,65] Typically, these are three-component reactions between an enoate or ynoate, aldehyde and a nucleophile. In the case of an enoate with an sp^2 Michael acceptor, the nucleophile is often eliminated, giving rise to MBH adducts without incorporation of the nucleophile. Initial work by Taniguchi and co-workers,[66] focused on the intermolecular reaction between α,ß-acetylenic ketones and a number of aldehydes in the presence of various reagents such as $TiCl_4$/TMSI, TMSOTf/TMSI, $TiCl_4$/Bu_4NI, TMSI/Bu_4NF, Et_2AlI, or TiI_4. Screening of conditions revealed the stoichiometric reagent combination $TiCl_4$/Bu_4NI as particularly effective in generating β-iodovinyl Baylis-Hillman adducts in good yield (Scheme 2-6).

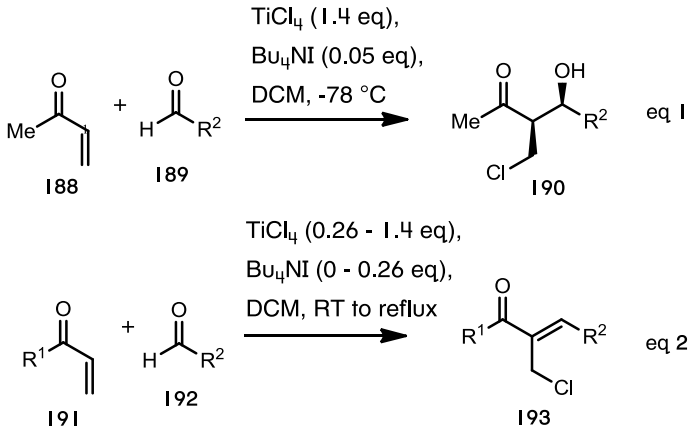
Following on from this initial pioneering research, Oshima and colleagues demonstrated that the same reagent combination could be used for the preparation of β-iodo aldol adducts **187** from the reaction between sp^2 Michael acceptors **185** and aldehydes **186**[67,68] (Scheme 2-6). As in the case of reductive aldol reactions, the nucleophile is incorporated in the final product whilst simultaneously creating a new chiral centre adjacent to the carbonyl group.

Scheme 2-6: A general intermolecular iodo-aldol reaction between Michael acceptors and aldehydes



Interestingly, a number of other research groups including Shi and co-workers[69] (Scheme 2-7, eq **1**) and Li et al.[70] (Scheme 2-7, eq **2**), have independently reported that using catalytic amounts of Bu_4NI results in the generation of chlorinated aldol-type adducts with traces or no iodo-aldol products detected. The reagent combination of $TiCl_4/Bu_4NI$ is considerably more complex than originally thought, with several reports of different reaction products dependent on the ratio of $TiCl_4$ to Bu_4NX (X = I, Br), reaction time and temperature. In general, higher reaction temperatures, longer reaction times and a catalytic or zero quantities of Bu_4NX favoured chlorinated aldol products **193** via elimination (Scheme 2-7, eq **2**).[64,69,71,72]

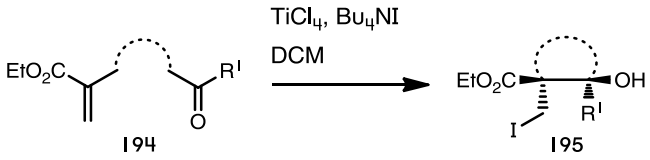
Scheme 2-7: Synthesis of chlorinated aldol products via the Baylis-Hillman reaction



Tandem iodo-aldol reactions have a number of strengths common to all MBH reactions; they have excellent atom economy and generate one, two, or three chiral centres from simple starting materials in a one-pot reaction: they allow enolate chemistry to be performed without the use of a strong base, are amenable to asymmetric catalysis, and the installed functional handle can be used for further

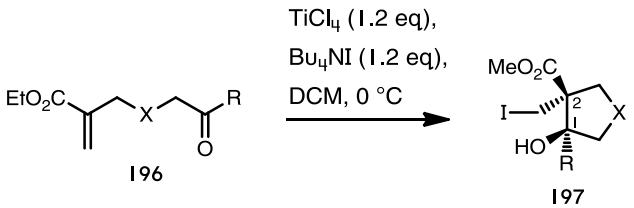
elaboration.[65] A limitation of iodol-aldol processes in general is their relative lack of application to the construction of quaternary centres important for natural product synthesis. The vast majority of examples reported in the literature use *mono-* or 1,2-disubstituted Michael acceptors as substrates, whereas quaternary centre construction will require a 1,1-disubstituted Michael acceptor such as **194** (Scheme 2-9). Although the iodo-aldol reaction has attracted the interest of several research groups, the intramolecular variant has not been studied in depth and there are only two reports in the literature.[65,73]

Scheme 2-8: Intramolecular iodo-aldol reaction for quaternary centre construction.



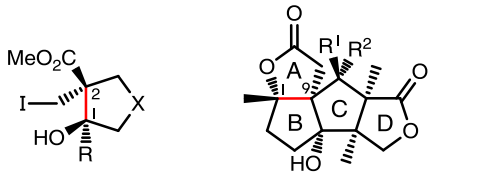
In a 2007 publication by the Greaney group,[65] an intramolecular iodo-aldol cyclization of 1,1-disubstituted alkenes was developed, affording hetero- and carbocycles containing quaternary centres. In this transformation, simple prochiral starting materials **196** were converted to cyclic alcohols **197** containing *vicinal* quaternary and secondary/tertiary stereocentres in good yields with excellent *anti-* diastereoselectivities with respect to the newly formed CH_2I and alcohol functional groups. (Scheme 2-9).

Scheme 2-9: Intramolecular iodo-aldol reaction for quaternary centre construction



Anislactones A/B were selected as a highly appropriate test of this iodol-aldol cyclisation methodology in the natural product arena and is devised to solve both the low yield of the alkylation and Mukaiyama aldol reactions in the previous model system (cf. Scheme 1-33). The *vicinal* C1 tertiary and C9 quaternary stereocentres of the AB-ring junction in anislactones A/B are analogous to the C1 and C2 stereocentres of **198** (Figure 2-3).

Figure 2-3: Reasoning for the adoption of an iodo-aldol cyclisation reaction in the synthesis of anislactones A/B



198

anislactone A. **2** R^1 = H, R^2 = OH

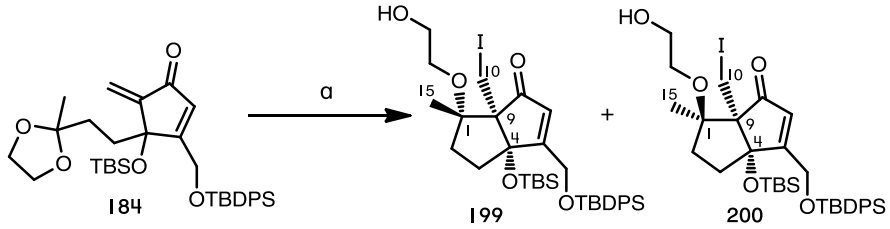
anislactone B. **3** R^1 = OH, R^2 = H

In the methodology presented by Greaney, the recently introduced iodomethyl group has an *anti*-relationship with the formed tertiary alcohol whilst in our system a *syn*-relationship would be required to allow the successful installation of the γ-lactone A-ring. The effect of a ketal as a replacement for the ketone in the iodo-cyclisation was unknown, but it was hoped this would result in the reversal of diastereoselectivity as required for the synthesis of anislactones A and B. Thus, 1,1-disubstitued **184** has all the elements of a suitable substrate for the iodo-aldol cyclisation and would allow us to examine the potential of this methodology on more complex systems.

With the crucial iodo-aldol cyclisation substrate in hand, we set about applying the previously developed iodo-aldol cyclisation methodology. To our delight, when a solution of Bu_4NI and $TiCl_4$ in DCM was treated with *exo*-methylene **184** in DCM at 0 °C, a separable 5:1 mixture of bicyclic diastereomers **199** and **200** was acquired in a good 79% overall yield. This one-pot reaction forms a new C–C bond between C1 and C9, creates a new five-membered ring and simultaneously

sets the stereochemistry of the triad of fully substituted chiral centres at C1, C9 and C4 (Scheme 2-10). The reaction is very robust and no problems were encountered during scale-up when conducting the reaction in multi-gram quantities.

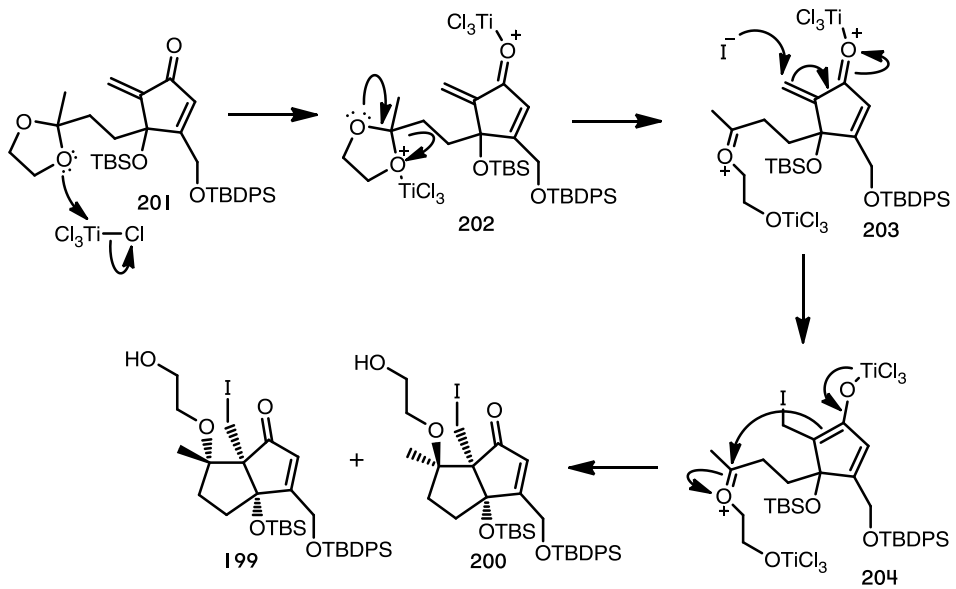
Scheme 2-10: Key intramolecular tandem iodo-aldol cyclisation reaction on ketal **184**



a) Bu_4NI, $TiCl_4$, DCM, RT, 79% combined, 63% **199** and 16% **200**, d.r. 5:1.

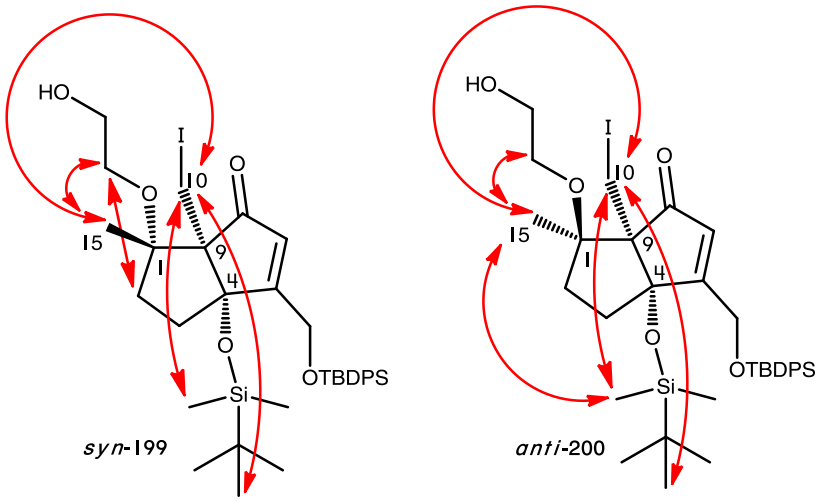
A plausible mechanism for this transformation is proposed in Scheme 2-11, which is similar to others reported in the literature for the intermolecular version of the iodo-aldol reaction.[67,68] Firstly, formation of **203** is obtained from the Lewis acid-mediated opening of the dioxolane moiety **202** leaving an oxonium ion. Subsequent 1,4-conjugate addition of iodide giving the *(Z)*-enolate **204** setting the scene for a 5-*exo*-trig cyclisation.

Scheme 2-11: Proposed mechanism for the intramolecular tandem iodo-aldol cyclisation



With both cyclisation products **199** and **200** isolated, we set about demonstrating their relative stereochemistries. Unfortunately, the use of X-ray crystallography proved unfeasible as both formed an oil on standing. Nonetheless, the elucidation of the relative stereochemistry was achieved by means of extensive 1D and 2D-NMR spectroscopy. Using 1D-^{1}H-NMR, ^{13}C-NMR and DEPT, as well as HSQC, HMBC and COSY 2D correlation spectroscopy, allowed us to assign all the proton and carbon signals observed for both diastereomers. This eventually permitted us to identify the cross peak interactions observed in the NOESY spectrum to specific and characteristic *through-space* interactions, and allowed us to determine the relative stereochemistry as outlined in Figure 2-4.

Figure 2-4: nOe interactions observed for iodo-aldol cyclisation products syn-**199** and anti-**200**

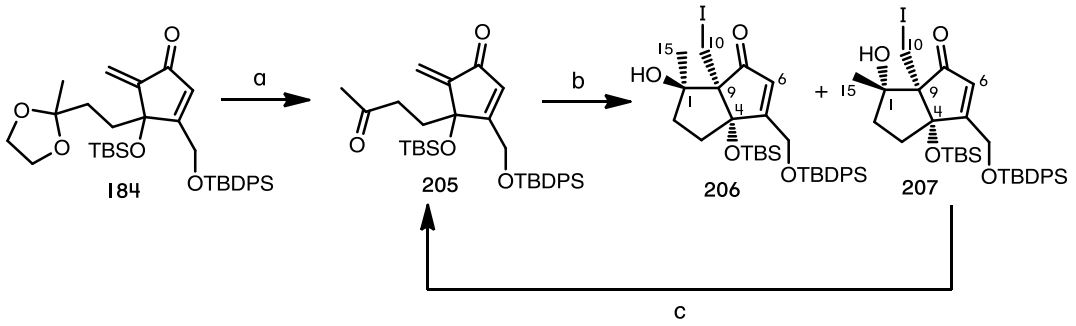


The crucial stereochemical configuration to be assigned was the orientation of the C15 methyl group and thus, the relative stereochemistry at C1. If we could demonstrate its location to be on the opposite face of ring B to the C10 methylene group, we would be able to simultaneously verify the correct orientation of ring B, due to the *cis*-arrangement of the formed BC ring junction. Therefore the key nOe interactions to be investigated are the presence of signal enhancements between the C15 methyl and the C10 methylene protons. It was hypothesised that if there was a *syn* relationship, then a nOe effect would be anticipated between C15 and

both C10 methylene protons. Starting with major diastereomer **199**, a 1D NOE difference experiment with pre-irradiation of the C15 methyl revealed a strong nOe signal enhancement to only a single C10 methylene proton. Additionally, we found no observed interactions between the C15 methyl and any of the methyl substituents of the TBS group. On the other hand, 1D NOE and 2D NOESY experiments revealed nOe effects between C10 and the TBS group at C4, suggesting the stereochemical assignments designated above. Further proof was obtained from the NOESY analysis of the minor diastereomer **200** which could be directly compared with **199**. Examination of the NOESY and 1D NOE difference data of minor diastereomer **200** revealed strong nOe effects between C15 and *both* C10 methylene protons that suggests these have a *syn*-stereochemical relationship. In addition, signal enhancements which were not observed in the NOESY analysis of **199** are now seen between C15 and methyl substituents of the TBS protected alcohol at C4. The direct comparison of the NOESY data from **199** and **200**, strongly aided our stereochemical assignments as indicated above.

A more expedient synthetic approach would be to perform the iodo-aldol cyclisation on diketone **205**, easily obtained by simple deprotection of dioxolane **184** (Scheme 2-12). This would remove the requirement for the previously developed ethyl iodide deprotection sequence[49] as the tertiary alcohol would be directly formed, reducing the synthesis by a single step. Treatment of ketal **184** with DDQ readily afforded diketone **205** in high yield. With the substrate for the iodo-cyclisation in hand, we applied the previously developed iodo-aldol methodology to **205** and to our delight, a separable 6:1 mixture of diastereomers **206** and **207** were formed in a combined yield of 70% together with the recovery of 25% of unreacted starting material.

Scheme 2-12: Key intramolecular tandem iodo-aldol cyclisation reaction on diketone **205**



a) DDQ, MeCN:H_2O (9:1), 40 °C, 92%; b) Bu_4NI, $TiCl_4$, DCM, RT, 84% combined, based on recovered starting material , 79% **206** and 5% **207**, d.r. 15:1; c) basic alumina, DCM, RT.

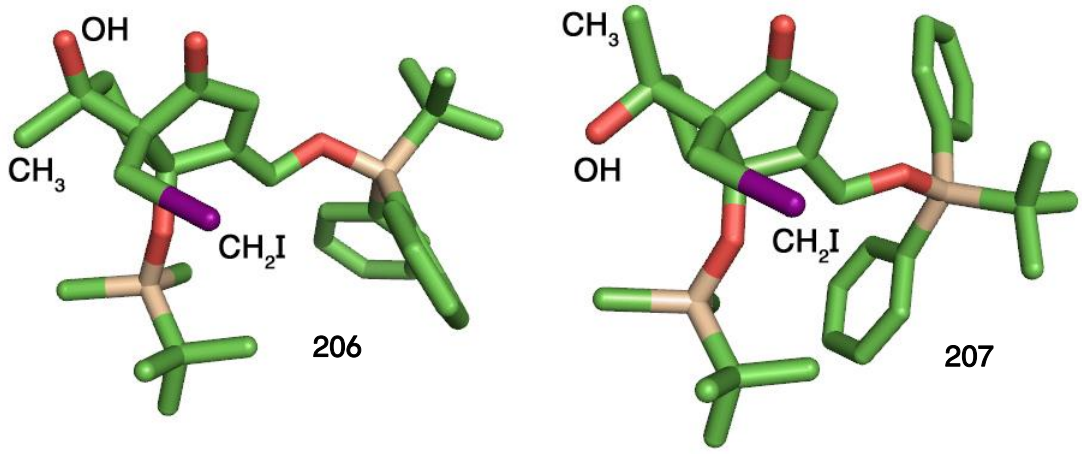
The ratio of diastereomers formed in the cyclisation reaction was easily established from the ^{1}H NMR of the crude reaction mixture *via* the integration of two singlets at δ_{major} 6.52 ppm and δ_{minor} 6.37 ppm corresponding to the alkene proton at C6. An interesting observation after purification by column chromatography was the contamination of major diastereomer **206** with a small but identifiable amount of substrate **205** even after repeated attempts at purification. Furthermore, the release of iodide was observed in purple coloured fractions containing **206** after column chromatography, implying that a retro-aldol process could be responsible for the conversion of **206** back to substrate **205**.

We decided to investigate if we could take advantage of this unexpected result and recycle the minor diastereomer **207**. A solution of **207** was exposed to basic alumina conditions at room temperature and monitored by ^{1}H NMR. Time-dependent formation of starting material **205** and disappearance of **207** was observed. After standing overnight, **207** was fully converted back to **205** with no observable side products. This was pooled with the previously recovered starting material and re-submitted to the iodo-aldol reaction conditions. A single attempt at recycling culminated in a 15:1 overall isolated diastereomeric ratio with **206** isolated in a combined 79% yield and a diminished 5% yield for **207**. It was not completely surprising that a retro-aldol event could occur with tertiary alcohols **206** and **207**, as

this was proposed as a possible explanation for the observed epimerisation at C1 in the previous model study (cf. Scheme 1-33).[49]

Pleasingly, tertiary alcohols **206** and **207** were formed as solids and on slow evaporation of the solvent, crystals could be formed. X-ray crystallographic analysis of diastereomers **206** and **207** enabled the unequivocal confirmation of their structures and relative stereochemistries, which were in agreement with the above stereochemical assignments as depicted above (Figure 2-5).

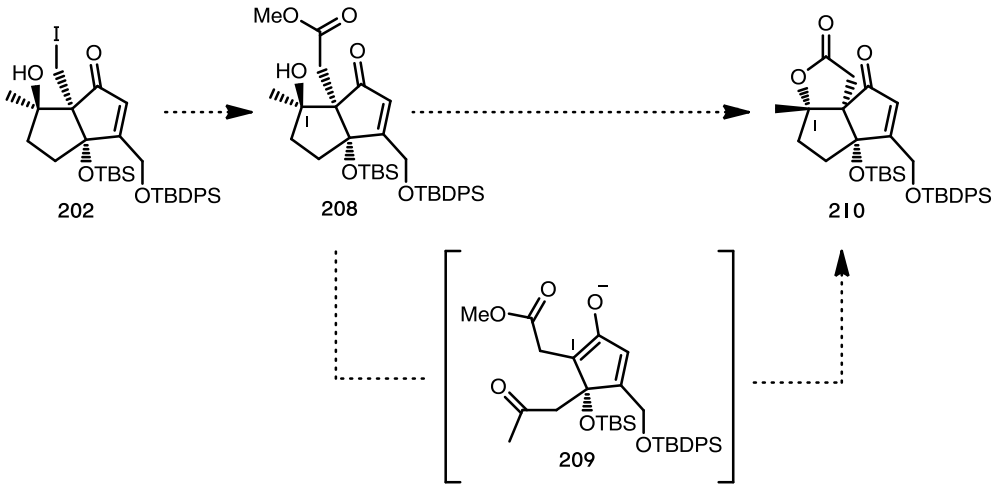
Figure 2-5: X-ray crystal structures for iodo-aldol diastereomers **206** and **207**



The crystal structure for major diastereomer **206** clearly shows a *syn* stereochemical relationship between the C15 methyl and the C10 methylene groups. As expected from the methodology published by the Greaney group,[65] the opposite was seen for the minor diastereomer **207** where the C15 methyl group is *anti* to the C10 methylene. The complete switch in diastereoselectivity with the diketone **205** as the substrate for the iodo-aldol cyclisation was not a complete disappointment. We envisaged a successful elaboration of the methylene iodide functional handle to ester **208,** after which the C1 tertiary alcohol is predicted to undergo a base induced retro-aldol/aldol equilibration, producing the required γ-lactone A-ring **210** via the epimerisation of C1 (Scheme 2-13). This anticipated retro-aldol/aldol equilibration has precedence in the previously observed C1 epimerisation event in the Greaney

model study[49] (Scheme 1-33) but is also a known phenomenon in the anislactone family of natural products.[12]

Scheme 2-13: Proposed synthesis of the tricyclic core of anislactones A/B via a retro-aldol process

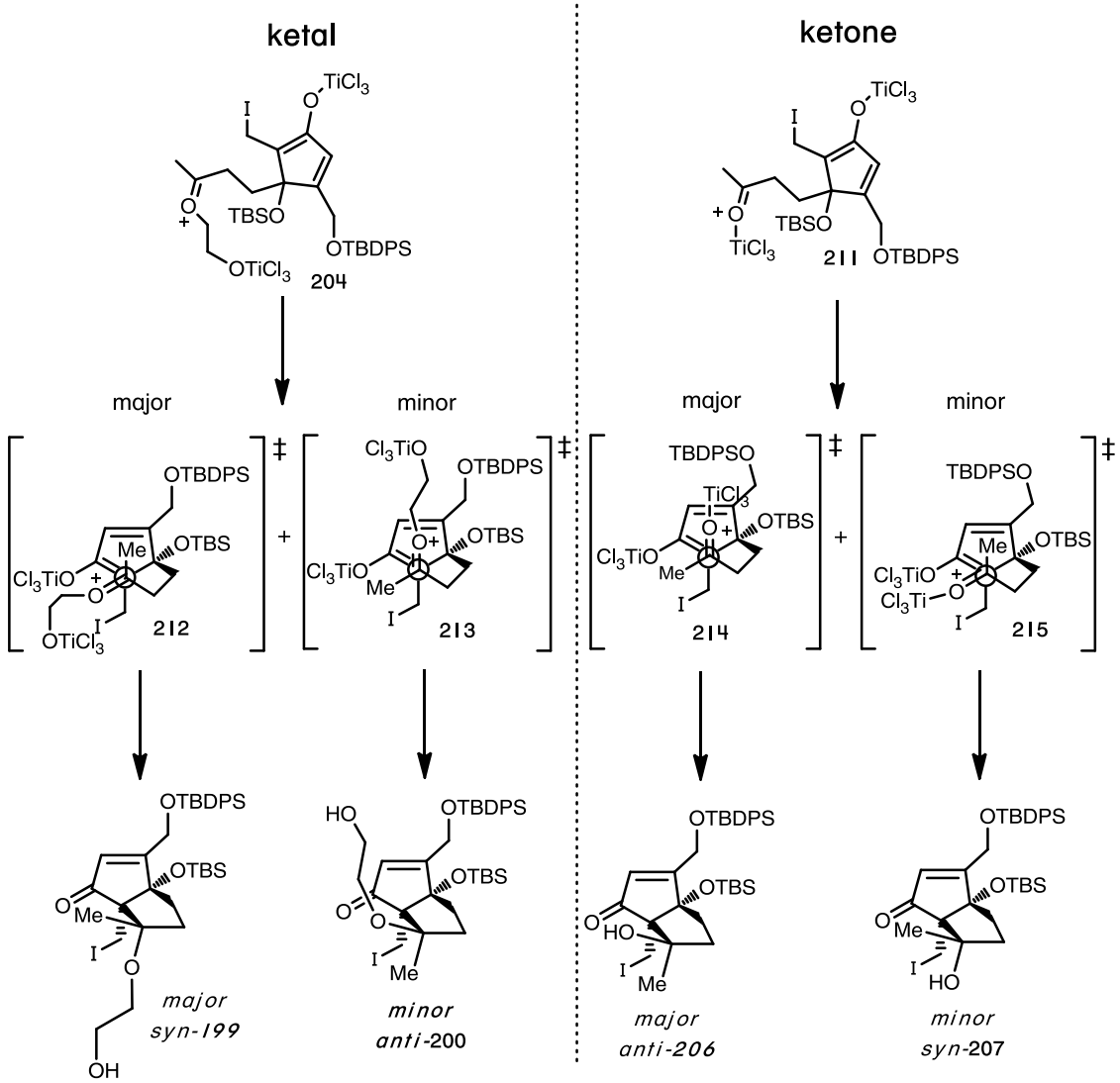


Such complete reversal in diastereoselectivity was attributed to the sensitivity of the transition state to the steric congestion around C1. The observed diastereoselectivity can be explained using the transition state models as outlined in Figure 2-6, which are based on initial conjugate addition of iodide generating a (*Z*)-enolate followed by a diastereoselective aldol reaction. In the case of the ketal substrate **204**, discrimination between transition states **212** and **213** is likely due to the orientation of the bulky ketal side chain, which is pointing away from the least hindered convex face in *syn*-**199** rather than pointing towards the more sterically crowded concave face in *anti*-**200**. The C15 methyl substituent is left pointing towards the concave face as it offers less steric congestion as compared to the bulkier ketal side chain. The highly differentiated concave and convex faces of the ensuing bicycle in **199** and **200** is what drives the observed diastereoselectivity leading to the preferential formation of *syn*-diastereomer **199** via the most stable transition state **212**.

The aldol reaction with methyl ketone **211** as the intermediate resulted in the complete reversal of diastereoselectivity. In this scenario, the C15 methyl group is

considered to be bulkier than the recently formed C1 tertiary alcohol, favouring transition state **214** with the methyl substituent aiming away from the convex face and the C1 alcohol pointing towards the concave space. This explains the reversed diastereoselectivity affording *anti*-**206** as the major diastereomer.

Figure 2-6: Proposed stereochemical model for the iodo-aldol cyclisation on ketal **204** and ketone **211**



In addition to the X-ray crystal structures, diastereomers **206** and **207** were fully characterised by the full suite of 1D and 2D-NMR spectroscopy techniques. With this set of characterisation data in hand, we were able to compare the NOESY data of both sets of diastereomers. Particular attention was again given to distinguishing

nOe interactions between C15 methyl and C10 protons. We noticed, for major diastereomer *syn*-**199** and minor diastereomer *syn*-**207**, the same specific nOe interaction between C15 and the same single C10 methylene proton. The same was seen for minor diastereomer *anti*-**200** and major diastereomer *anti*-**206** where nOe cross peak interactions were seen between C15 and *both* C10 methylene protons. Together, these observations strongly supported our original stereochemical assessments based on 2D-NOESY and 1D-NOE analysis for diastereomers *syn*-**199** and *anti*-**200.**

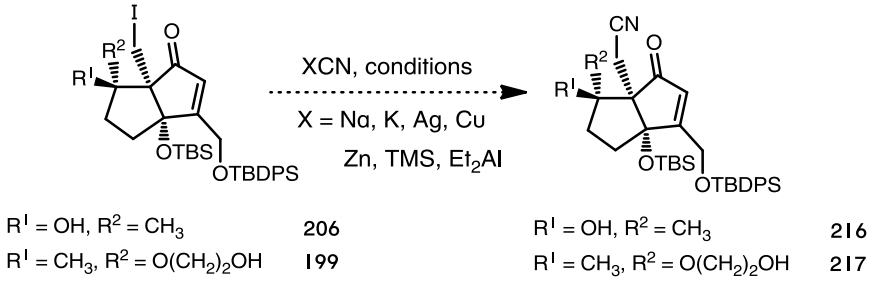
2.3.5 Attempts at elaboration of the BC bicyclic core

With an efficient synthesis of the bicyclic anislactone cores **199** and **206** established, we investigated the potential for further elaboration with the aim of installing the A-ring γ-lactone. We wanted to perform a one-carbon homologation reaction on the recently introduced iodide functional handle. Initial attempts focused on the potential of a cyanide-iodide exchange with **199** and **206** using a variety of cyanide sources (Figure 2-7). Starting with **206**, we were disappointed to observe only unreacted starting materials and retro-aldol product **205**. Given the previously observed propensity for **206** to undergo a retro-aldol process (cf. Scheme 2-12) it certainly was not a surprise to witness its reoccurrence.

Next, we shifted our attention to substrate **199**, which as a result of containing a protected tertiary alcohol is not anticipated to be susceptible to a retro-aldol reaction. Consequently **199** would be more stable than **206** to a greater variety of reaction conditions. First attempts began with the Kolbe synthesis of nitriles using NaCN or KCN in a variety of polar solvents.[74,75] Unfortunately, no formation of the desired product **217** was achieved at room or elevated temperatures; no reaction and cleavage of the silyl protecting groups at high temperatures was observed. Then we examined the potential of AgCN, CuCN and ZnCN, but could only observe the slow decomposition of the starting materials with no detectable product

formation. Final attempts using TMSCN and Et_2AlCN resulted in the same disappointment; with quantitative recovery of starting materials. At this point, investigation into the cyano-iodide exchange was abandoned and other possibilities were examined.

Figure 2-7: Screening of different cyanide sources for the one-carbon homologation of **199** and **206**



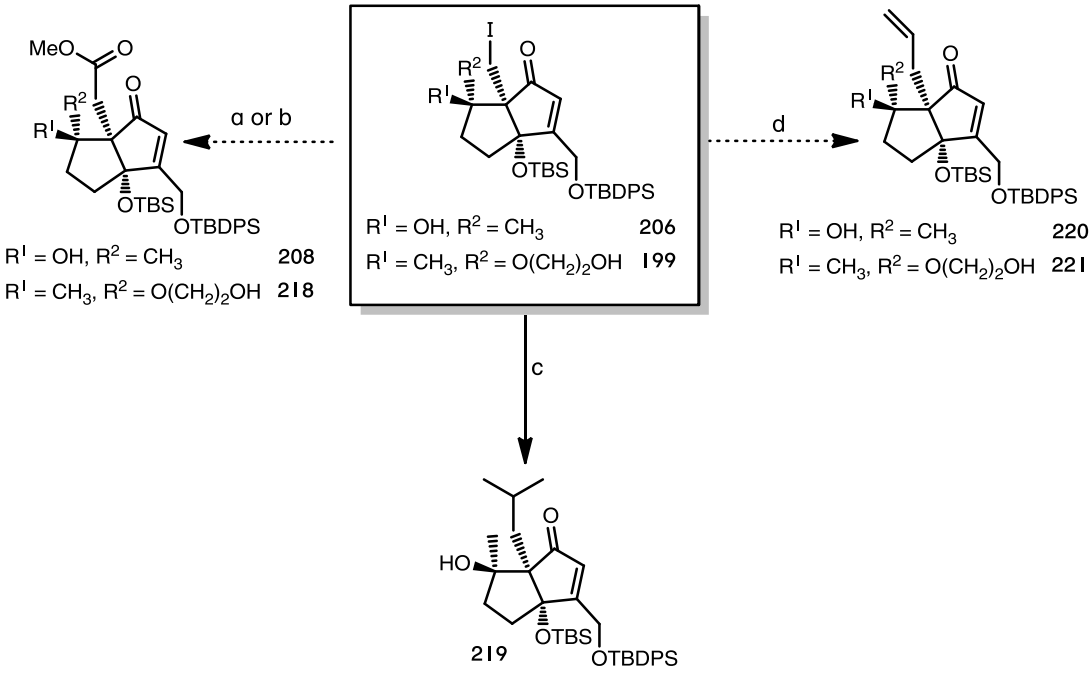
R^I = OH, R^2 = CH_3 **206**
R^I = CH_3, R^2 = $O(CH_2)_2OH$ **199**

R^I = OH, R^2 = CH_3 **216**
R^I = CH_3, R^2 = $O(CH_2)_2OH$ **217**

Cyanide Source	Conditions	Result
NaCN or KCN	MeOH, DMSO, DMF, THF, H_2O as cosolvent, RT to reflux	**199**: No reaction or TBS/TBDPS deprotection
		206: Retro-aldol product
AgCN	MeOH, toluene DMSO, DMF, Et_2O, THF, H_2O as cosolvent, RT to reflux	**199**: SM and decomposition
		206: No reaction or retro-aldol product
CuCN or ZnCN	MeOH, DMSO, DMF, THF, H_2O as cosolvent, RT to reflux	**199**: SM and decomposition
		206: No reaction or retro-aldol product
TMSCN	Toluene, MeOH, THF, H_2O as cosolvent, RT to reflux	**199**: No reaction
		206: Retro-aldol product
Et_2AlCN	Toluene, DCM, RT to reflux	**199**: No reaction
		206: Retro-aldol product

Moving forward, we decided to explore a diverse range of reactions to further elaborate substrates **199** and **206**, which are summarised in Figure 2-8.

Figure 2-8: Attempts at a one-carbon homologation of substrates **199** and **206**



a) Mg turnings, I_2 or 1,2-dibromoethane, $CO(OMe)_2$ or ClCO(OMe), Et_2O or THF, RT to 50 °C; b) $Pd(PPh_3)_4$ (10 mol%), CO (balloon pressure) or bubbled into reaction, NEt_3, hv (pyrex or quartz, 254 nm), methanol, RT; or allyltributyltin, AIBN, NEt_3, methanol, 80 °C; or $(Bu_3Sn)_2$, ClCOOMe, methanol, hv (pyrex or quartz, 254 nm); c) *i*-PrMgCl·LiCl, THF, RT; d) vinylmagnesium bromide, THF, RT.

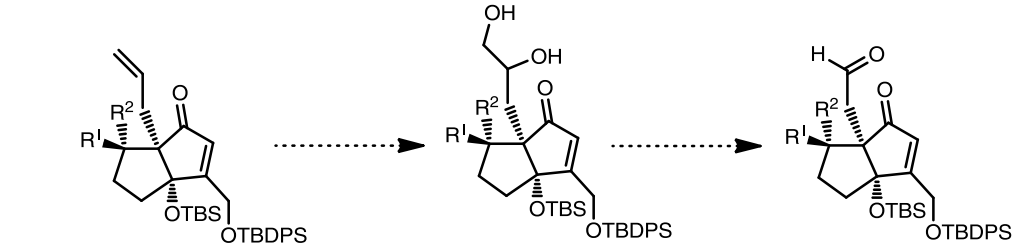
We began by exploring the possibilty of Grignard formation with either **199** or **206** followed by quenching with an electrophile such as methyl chloroformate or dimethyl carbonate. Unfortunately, no desired product was detected, only starting materials were recovered for **199**, and **206** was completely converted back to retro-aldol product **205**. Careful monitoring of the reaction via LCMS at the stage of Grignard formation revealed the Grignard had not formed and only starting material was detected.

Next, we investigated the use of Knochel's procedure for Grignard generation.[76] Treatment of **206** with *i*-PrMgCl·LiCl at –78 °C yielded no reaction but upon warming to RT resulted in the clean and rapid formation of an S_N2 type product **219** in almost quantitative yield. The concentration of the reaction was an important factor in this process and it had to be conducted at 20 mM; more dilute conditions directed the reaction towards the retro-aldol product **205** with no traces of

isopropyl **219** detected by TLC or LCMS. The synthesis of **219** is an interesting result relative not only to the limited success we had with the cyanide-iodide exchange, but is due to the steric bulk of the isopropyl nucleophile and the absence of any retro-aldol product **205**. A plausible explanation for this is that this process occurred by a radical-type reaction, which is known to have low sensitivity to steric hindrance and is a recognised phenomenon in Grignard formation of alkyl halides with magnesium metal.[77] Nonetheless, the unexpected compound **219** did not have the required functionality to move forward in the synthesis and so had to be abandoned.

We postulated that if we could functionalise with the hindered *i*-PrMgCl·LiCl then a similar success would be predicted for vinylmagnesium bromide. Introduction of a vinyl group would allow further elaboration to the required aldehyde via a dihydroxylation/oxidative cleavage sequence (Scheme 2-14).

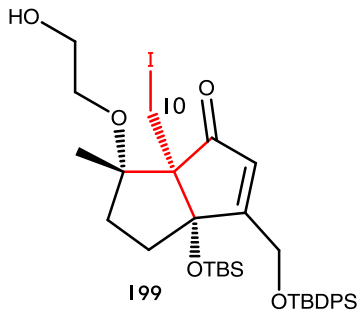
Scheme 2-14: Proposed possible elaboration of iodo-aldol cyclisation products



This would provide aldehydes **224** and **225** of which **224**, with its naked tertiary alcohol, would be expected to undergo a base-induced retro-aldol/aldol equilibration resulting in lactolisation, similar to the epimerisation observed in the model study (Scheme 1-33).[49] We were perplexed to find that after applying the same reaction conditions optimised for *i*-PrMgCl·LiCl, we could not obtain either **220** or **221**. Screening of many conditions resulted in the identification of starting materials or retro-aldol **205** as the only artefacts of the reaction. We suspected the lack of reactivity observed for these two substrates could stem from the high steric

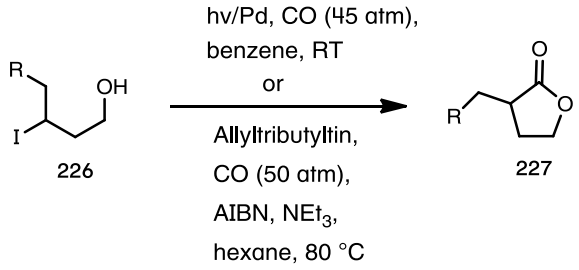
congestion around C10. In fact the vicinity around the electrophilic reactive site at C10 is structurally similar to neopentyl iodide (Figure 2-9) which is notorious for being unreactive especially to S_N2-type processes.[75] The steric encumbrance around C10, which is adjacent to a quaternary stereocentre would block any approaching nucleophile in an S_N2 type reaction.

Figure 2-9: Highlighted is the structural similarity between **199** and neopentyl iodide



With this in mind we turned our attention to free radical chemistry which unlike ionic-type reactions is relatively less sensitive to steric hindrance. We explored an ambitious atom transfer carbonylation approach that would lead to methyl esters **208** and **218.** Carbonylation reactions of primary alkyl iodides are acknowledged in the literature but these tend to be sluggish compared to their secondary and tertiary counterparts.[78,79] For this transformation there are two competing approaches, photoirradiation or thermal initiation. Ryu and colleagues reported the carbonylation of alkyl iodides **226** in an autoclave with photoirradiation in the presence of a Pd catalyst and pressurised carbon monoxide.[78] Equally as effective are the thermal initiation conditions developed by Komatsu and co-workers that included the reagent combination of allyltributyltin, AIBN and 50 atm carbon monoxide (scheme 2-16).[80]

Scheme 2-16: Intramolecular synthesis of lactones via atom transfer carbonylation methods



We attempted to replicate these conditions, but due to the absence of an autoclave, we performed the reactions with only balloon pressure of carbon monoxide. A Rayonet photochemical reactor was used with its emission centred at around 254 nm and a pyrex or quartz filter was applied. To our dismay, only substrate decomposition or retro-aldol product was detected for substrates **199** and **206**. Study of the literature revealed these types of reactions have much better success with more reactive substrates such as aryl halides, allyl halides and benzylic halides,[81-84] which could be accomplished sometimes under just atmospheric pressure of carbon monoxide. Therefore it was not a complete surprise that these reactions were ineffective.

Additionally, we examined photoirradiation of bis(tributyltin) and instead of carbon monoxide, methyl chloroformate was used as a carboxyl radical acceptor,[85-87] but this only afforded similar results with no traces of product identified by LCMS. As is evident from the outcome of these reactions, further elaboration of iodo-aldol products **199** and **206**, was not as straightforward as expected. We attributed the low reactivity at C10 to the extreme steric congestion making any type of nucleophilic displacement process near impossible. It was at this stage that we decided to consider a cyano-aldol as a replacement for the iodo-aldol cyclisation, which would introduce the required functionality to install the γ-lactone. Due to the advanced nature of *exo*-methylene **184** its availability was limited and for that reason, we chose to resynthesise starting materials. This provided the opportunity to develop a more efficient route to starting materials that would deal with the protecting group issues previously discussed (cf. Section 2.3.2). NMR characterisation spectra for select compounds along this route are presented in the appendix.

3 Synthesis of the Tricyclic Cores of Anislactones A/B and Merrilactone A

A cyanide variant of the iodo-aldol cyclisation reaction was investigated after the shortcomings of attempts at further functionalising iodo-aldol products **199** and **206**. In contrast to having iodide as the nucleophile, cyanide will, in one-pot, install the necessary functionality to deliver the γ-lactone A-ring without any need for further carbon homologation. Additionally, if left in place during the ethyl iodide deprotection sequence, the cyanide could undergo *in situ* lactonisation/hydrolysis without any need for a pre-hydrolysis to the carboxylic ester. Incorporating the cyano-aldol reaction into the synthesis did not require any significant modifications to the original retrosynthesis but it did, however, provide an ideal opportunity to improve our route to starting materials.

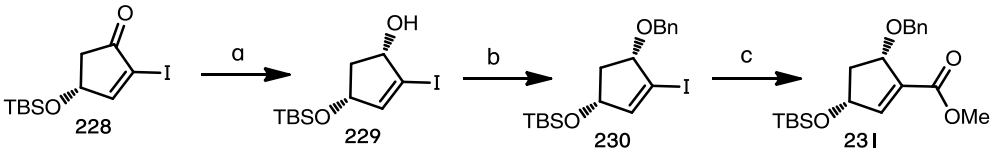
3.1 Morita–Baylis–Hillman Route to Cyclopentenone Starting Materials

Although our previous route to cyclopentenone intermediate **173** was successful, it was not as efficient as we would have liked, since it was plagued with regioselectivity protection issues and purification problems during scale-up. We first attempted to address these issues by adapting methodology previously used by Nicolaou and co-workers in their total synthesis of sporolide B (Scheme 3-1).[88]

In Nicolaou's synthesis, the Luche reduction[89] of enantiomerically pure iodoenone **228** afforded **229** and after subsequent benzylation, gave vinyl iodide **230** in excellent yield. Next, a carboxymethylation of the latter compound under palladium-catalysed conditions and balloon pressure of carbon monoxide led to methyl ester **231**. It was this final transformation that grabbed our attention, since this could be applied to our own synthesis which would allow the stepwise

introduction of both allylic alcohols, eliminating any requirement for regioselective alcohol protection.

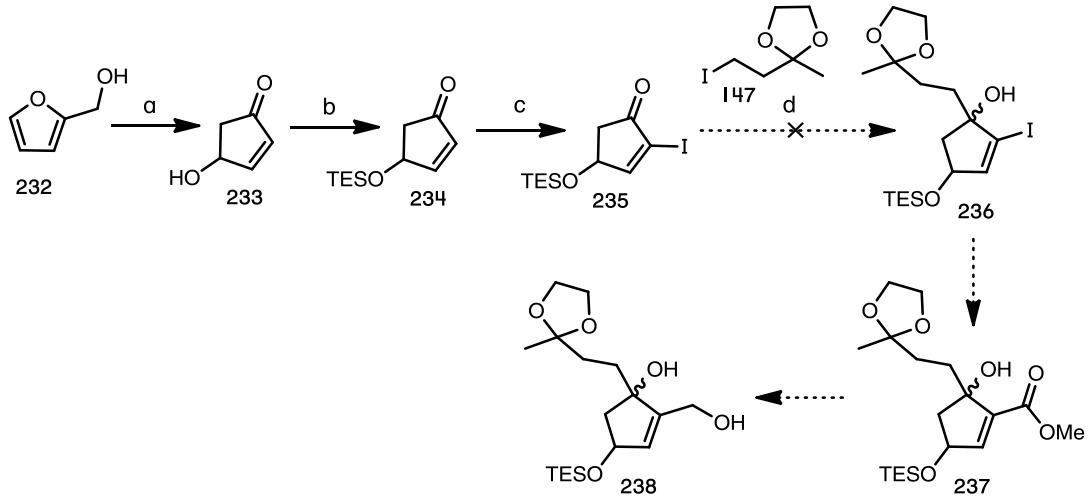
Scheme 3-1: Functionalisation of **228** by Nicolaou et al. in the synthesis of sporolide B



a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, –78 °C; b) BnBr, NaH, THF, 0 °C, 95% (two steps); c) $[PdCl_2(PPh_3)_2]$, NEt_3, CO (balloon pressure), MeOH, 70 °C, 95%.

In our attempt at implementing this methodology, we started with the acid-promoted Bac-Piancatelli[90] rearrangement of commercially available furfuryl alcohol **232**, forming cyclopentenol **233**, which after subsequent protection as the TES ether under standard conditions, yielded **234** in 48% yield over two steps (Scheme 3-2).[91] Next, α-iodination[88,92] of **234** by means of iodine in DCM:pyridine resulted in the formation of iodoenone **235**. Unfortunately repeated attempts at the addition between iodoacetal **147** and iodoeneone **235** under conditions previously demonstrated (cf. Scheme 2-5) were unsuccessful. A mixture of unidentifiable products was seen and no product could be isolated cleanly form the reaction mixture. The presence of the iodide functional group in the substrate likely complicated matters as it too could undergo lithium exchange with the formed organometallic nucleophile leading to a multitude of undesirable side-reactions. This was a major disappointment since it was anticipated that, had the key addition been effective, the subsequent palladium-catalysed carbonylation and ester reduction would have been relatively straightforward.

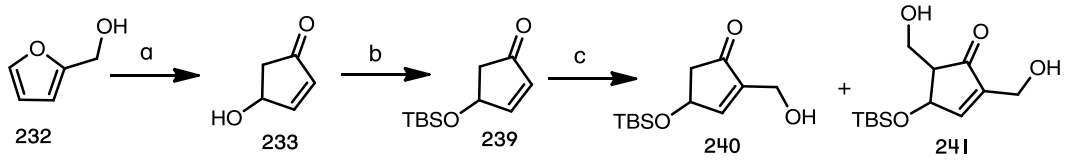
Scheme 3-2: Attempted new route to starting materials via a palladium-catalysed carbonylation reaction



a) hydroquinone, sodium phosphate buffer, 1,4-dioxane, H_2O, pH 4.1, reflux, 60%; b) TESCl, DMAP, NEt_3, DCM, RT, 80%; c) I_2, DCM:Pyridine, RT, 57%; d) **147** ^{t}BuLi, Et_2O, –78 °C.

Fortunately, success was later achieved with the Morita–Baylis–Hillman[64,93,94] reaction of **239** obtained from the TBS protection of the Bac-Piancatelli rearrangement product **233** (Scheme 3-3). Modified conditions from the work of Gatri and El Gaied[95] were adopted for the MBH reaction. Gratifyingly, exposure of **239** to imidazole and excess formaldehyde over 6 days at room temperature resulted in the formation of primary alcohol **240** in moderate yield with a small amount of unwanted dialkylated by-product **241**. The extended reaction time was necessary to achieve the reported yields and any attempts to accelerate the reaction via elevating the temperature only resulted in the attenuation of **240**.

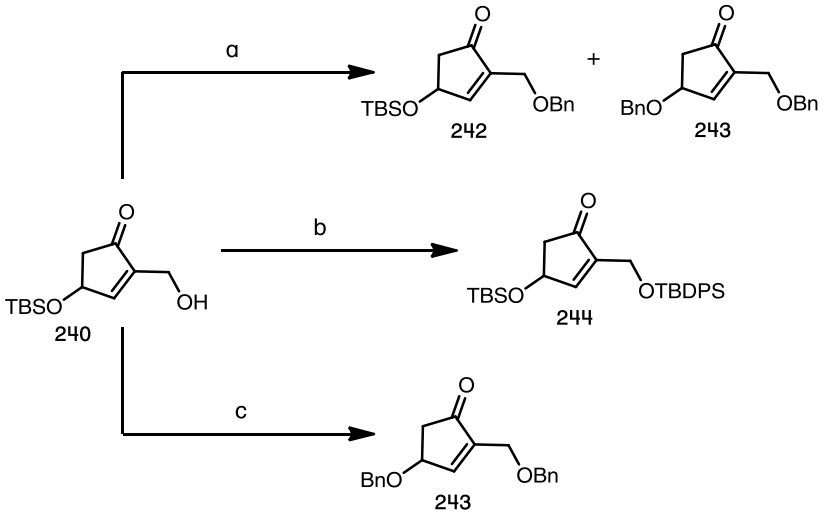
Scheme 3-3: Morita–Baylis–Hillman route to starting materials



a) hydroquinone, NaH_2PO_4, H_2O, 1,4-dioxane, pH 4.1, reflux, 60%; b) TBSCl, DMAP, NEt_3, DCM, reflux, 85%; c) HCOH, imidazole, THF:H_2O (1:1), RT, 40% **240** and 11% **241** .

Next, we attempted a protection of the most recently formed primary alcohol with an orthogonal benzyl protecting group (Scheme 3-4). Previous experience with substrate decomposition directed us towards introduction of the benzyl group under neutral or acidic conditions rather than the relatively harsh basic conditions of the Williamson ether synthesis (cf. Section 2.3.2). In addition to benzyl trichloroacetimidate,[53,54] we examined the feasibility of using 2-benzyloxy-1-methylpyridinium triflate,[96] a reagent used for benzyl protection under comparatively neutral conditions. However, in our hands both methods were ultimately unsuccessful with either poor conversion to the desired benzyl-ether **242** or *bis*-benzylated **243** as the only isolatable product. Under both conditions, *bis*-benzylated **243** by-product was obtained suggesting that the reaction conditions must have been sufficiently acidic to cleave the TBS group *in situ* with subsequent re-protection as the benzyl ether.

Scheme 3-4: Attempts at protection of the primary alcohol



a) **Method A:** 2-benzyloxy-1-methylpyridinium triflate, MgO, $PhCF_3$, 85 °C, 15% **242** and 50% **243**; b) TBDPSCl, imidazole, DMAP, DMF, RT, 74%; c) **Method B:** benzyl trichloroacetimidate, TfOH, cyclohexane:DCM (2:1), RT, 16%.

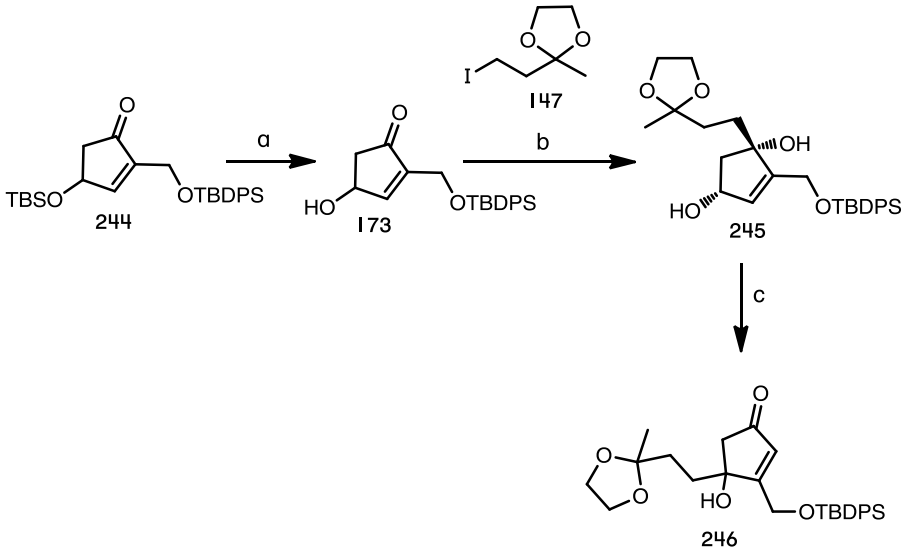
This set of results directed us to select the TBDPS group due to its robust stability, as its removal was planned much later towards the end of the synthesis and the ability to deprotect the TBS ether in its presence under mildly acidic conditions.

Therefore, simple protection of the allylic alcohol as a TBDPS ether provided cyclopentenone **244** in an overall yield of 14% over 4 steps. Even with the moderate yield of the MBH reaction, this synthetic sequence offers considerable advantages over the previous cyclopentenone-diol route (Section 2.3.2). Firstly, the overall number of steps in the sequence is reduced by two and more importantly the MBH reaction was ideal for scale-up; multigram batches of crude product could be pooled together and purified without difficulty.

3.2 Synthesis of the Cyano-Aldol Cyclisation Substrate

At this juncture, we decided to attempt to remove the TBS group first and then perform the key addition step on the free alcohol **173** (Scheme 3-5). This order of transformations was chosen to avoid ketal deprotection during the DDQ-mediated TBS removal.[97] We were pleased to find that treatment of **251** with DDQ[63] brought about the clean deprotection of the TBS ether and left the TBDPS group untouched furnishing secondary alcohol **173** in 85% yield. We were now set for the key addition which began with the generation of the organometallic nucleophile from iodoketal **147** and *tert*-butyllithium in Et_2O at –78 °C. This was later transferred to a solution of **173** at –78 °C, resulting in the formation of tertiary alcohol **245** in good yield as an inseparable 6:1 mixture of diastereomers. At present, the facial selectivity of the addition could not be confidently determined from the analysis of the 2D-NOESY spectrum. However, the assignments indicated below in Scheme 3-5 were based on the elucidation of stereochemistry at a later stage *(vide infra)* and were assigned retrospectively (cf. Section 3.5.3). Subsequent DMP oxidation of the secondary alcohol **245** afforded enone **246** in excellent yield.

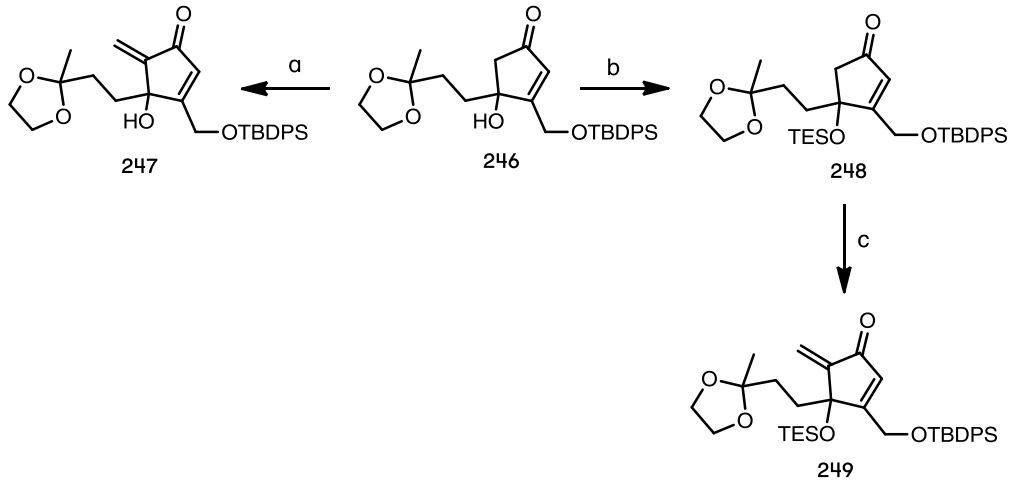
Scheme 3-5: Key nucleophilic addition and synthesis of tertiary alcohol intermediate **246**



a) DDQ, THF:H_2O (9:1), 40 °C, 85%; b) **147**, ^{t}BuLi, Et_2O, –78 °C to RT, 72%, d.r. 6:1; c) DMP, $NaHCO_3$, DCM, RT, 92%.

Next, we investigated the potential of performing the methylenation on **246** using Eschenmoser's salt with the free alcohol, but unfortunately even after numerous attempts at chromatographic purification, we could only obtain an impure mixture of **247** and unreacted starting material **246** in an approximate yield of 27% (Scheme 3-6). Moving forward, we decided upon TES protection of the sterically hindered tertiary alcohol using the reactive TESOTf in DMF at RT which afforded **248** in excellent yield. Methylenation of **248** using Eschenmoser's salt in THF at –78 °C to RT, followed by elimination of the Mannich base product with *m*CPBA[98] gave the desired *exo*-methylene **249** in 85% yield over two steps.

Scheme 3-6: *Exo*-methylene formation using Eschenmoser's salt



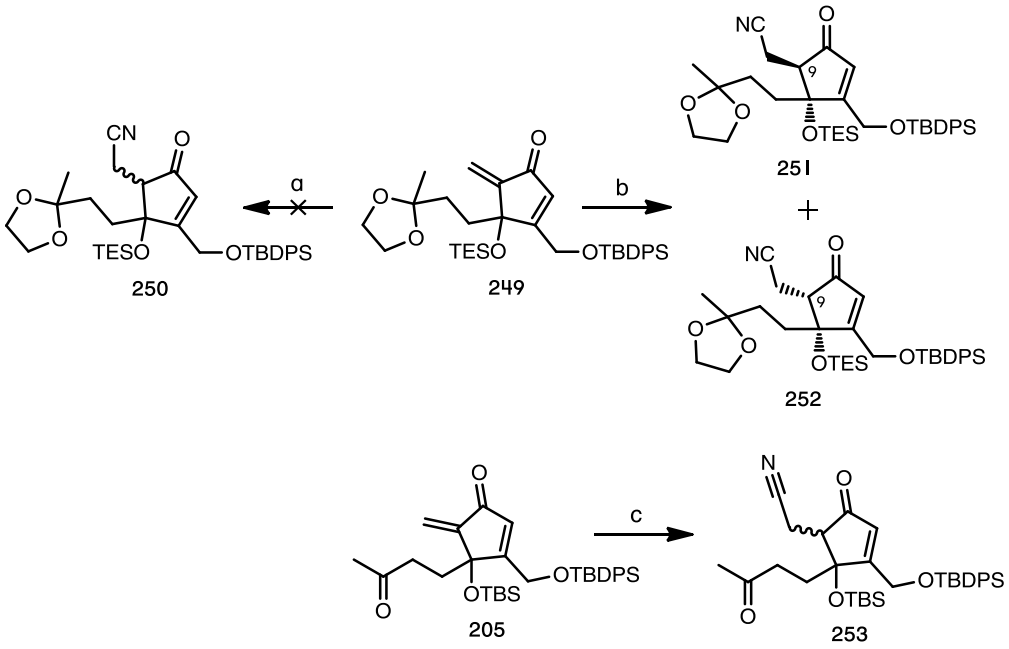
a) i) LDA, $[CH_2=NMe_2]^+ I^-$, THF, –78 °C to RT; ii) *m*CPBA, DCM:$NaHCO_3$ (2:1), RT, 27% (two steps); b) TESOTf, 2,6-lutidine, DMF, RT, 88%; c) i) LDA, $[CH_2=NMe_2]^+ I^-$, THF, –78 °C to RT; ii) *m*CPBA, DCM:$NaHCO_3$ (2:1), RT, 85% (two steps).

3.3 Intramolecular Cyano-Aldol Cyclisation Reaction

Although halo-aldol MBH-type processes have generated much chemical interest, there has been no reported examples of cyano-tandem aldol or MBH-type processes in the literature making this transformation of particular interest. We first had to select an appropriate cyanide source for the conjugate addition and decided to familiarise ourselves with the Michael addition before attempting the cyclisation. Our first effort using tetrabutylammonium cyanide resulted in no observable reaction with full recovery of starting materials (Scheme 3-7). Switching to diethylaluminium cyanide, a reagent used in the Nagata hydrocyanation reaction,[99] immediately garnered success affording a 1.1:1 separable mixture of diastereomers **251** and **252**, in a combined yield of 66%. The NOESY spectrum for **251** revealed strong correlation peaks between the single proton at C9 and the methylene protons of the TES protecting group. The absence of such interactions for **252** established the relative stereochemistry at C9 for both diastereomers and confirmed the stereochemical assignments given below. Next, we attempted the same procedure on ketone **205** which yielded the Michael adduct **253** as the only diastereomer. No

traces of cyano-aldol cyclisation products were detected by TLC or LCMS in any of these examples. This demonstrates that a strong Lewis acid such as $TiCl_4$ is required to activate the ketone/ketal for the intramolecular cyclisation to proceed.

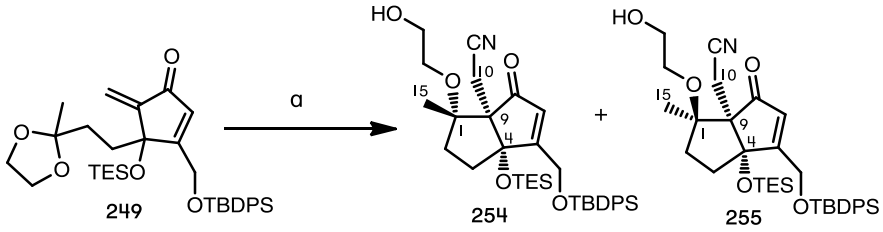
Scheme 3-7: Examination of the feasibility of a cyano 1,4-conjugate addition reaction



a) Bu_4NCN, DCM, RT; b) Et_2AlCN, DCM, RT, 66%, d.r. 1.1:1; c) Et_2AlCN, DCM, RT, 57%.

We attempted the cyano-aldol cyclisation using the same procedure used in iodo-aldol cyclisation (cf. section 2.3.4) but replacing tetrabutylammonium iodide with diethylaluminium cyanide. Interestingly, this only led to rapid decomposition of the substrate to a complex mixture of unidentifiable products. Knowing the cyano conjugate addition proceeded well with the substrate **249** in the absence of $TiCl_4$ as a Lewis acid, we decided to modify the procedure by changing the addition order of $TiCl_4$ and diethylaluminium cyanide. First, treating a solution of **249** in toluene at 0 °C with diethylaluminium cyanide, followed in 10 mins by the addition of a solution $TiCl_4$ in toluene, resulted in a separable 15:1 diastereomeric mixture of **254** and **255** with a good overall yield of 77% (Scheme 3-8).

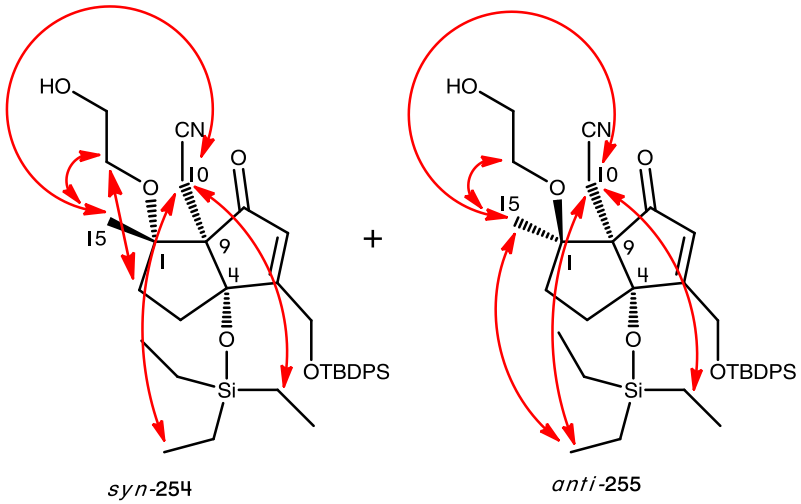
Scheme 3-8: Key intramolecular tandem cyano-aldol cyclisation reaction



a) Et_2AlCN, $TiCl_4$, toluene, 0 °C, 77% combined, 72% **254**, 5% **255**, d.r. 15:1.

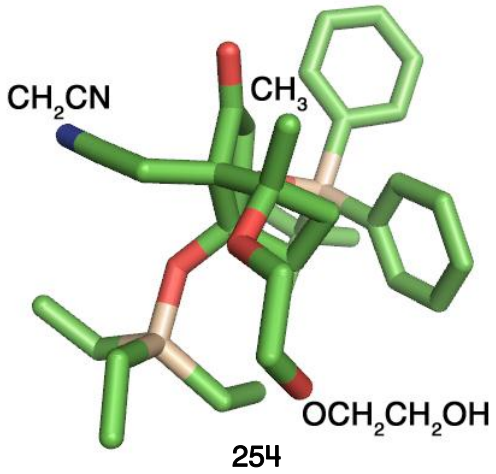
The diastereoselectivity for the cyclisation was expected to be the same as the iodo-aldol cyclisation with ketal **184** as the substrate (cf. Scheme 2-10), and indeed this was the case. Analysis of the 2D NOESY data of *syn*-**254** revealed nOe signal enhancements between C15 and a single C10 methylene proton, which is in agreement with the previous NOESY data obtained for *syn*-**199**. Likewise, NOESY analysis of *anti-255* showed strong nOe effects between the C15 methyl and *both* the C10 methylene protons, which closely matches the nOe signal enhancements observed with *anti*-**200** (Figure 3-1).

Figure 3-1: nOe signals observed for cyano-aldol cyclisation products *syn*-**254** and *anti*-**255**



With major diastereomer **254** isolated as a solid, we were fortunate enough to obtain single crystals after slow evaporation, which were used for X-ray crystallographic analysis (Figure 3-2).

Figure 3-2: X-ray crystal structures for cyano-aldol product **254**



254

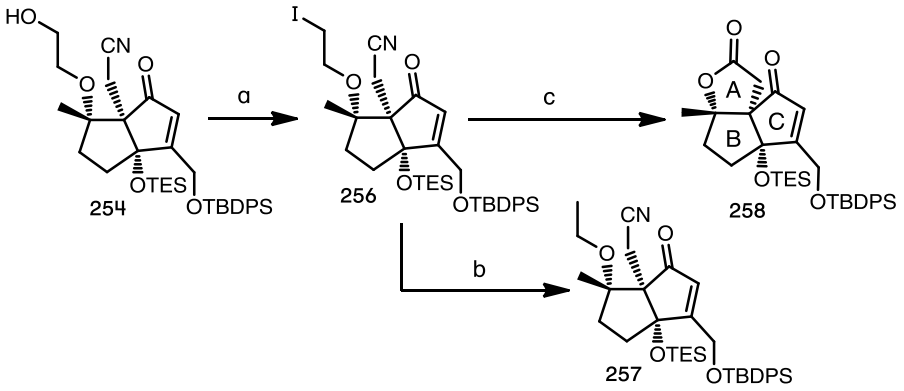
The crystal structure for major diastereomer **254** visibly shows the desired *anti* stereochemical relationship between the C15 methyl and the C10 methylene groups. No crystalline forms could be obtained for minor diastereomer **255** as it is a viscous oil. Even without a crystal structure for **255**, the extensive NOESY analysis of both diastereomers combined with the conclusive proof from the X-ray crystal structure of the other diastereomer **254**, undoubtedly confirmed the stereochemical assignments given above.

The triad of stereocentres at C1, C4 and C9 have now been installed with the required relative stereochemistry. Incorporation of the cyanide functional handle in **254** during the key cyclisation was intended to side-step the problems encountered with the one-carbon homologation attempts of **199** and **206** (cf. Section 2.3.5). It was anticipated that the introduced cyanide functional handle would be more open to further elaboration. Its susceptibility to hydrolysis would allow the simple formation of the desired γ-lactone A-ring.

3.4 In-Situ Lactonisation to Tricyclic ABC Core of Anislactones A/B

Turning our attention to the installation of the γ-lactone A-ring, we decided to press forward in the synthesis with bicycle **254**. We first wanted to explore the prospect of leaving the cyano group in place to undergo an *in situ* cyclisation/hydrolysis during the ethyl iodide deprotection sequence. Functional group conversion of **254** from the primary alcohol **254** to ethyl iodide **256** proceeded smoothly leading us to attempt the one-pot ethyl iodide deprotection and *in situ* lactonisation sequence. We first attempted the ethyl iodide deprotection in the absence of water, which meant the only products we would expect to observe are the tertiary alcohol or cyclisation to an imidate. Interestingly, only reduction product **257** and unreacted starting material were observed with no trace of lactone **258** or the formation of an imidate (Scheme 3-9).

Scheme 3-9: Synthesis of the tricyclic core of anislactones A/B

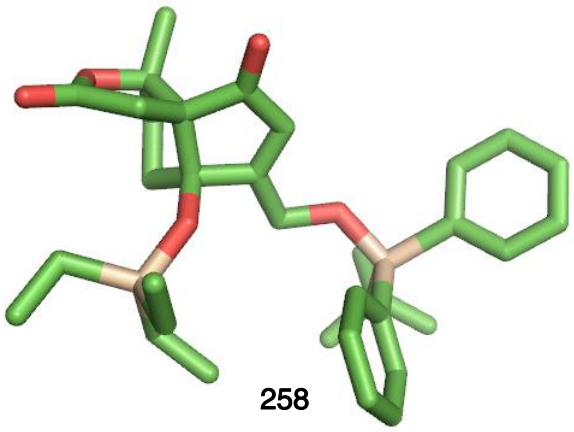


a) I_2, imidazole, PPh_3, DCM, RT, 94%; b) Zinc dust,[100] MeOH, 50 °C, 44%; c) Zinc dust,[100] THF:0.1 M AcOH (9:1), reflux, 89%.

Our efforts then focused on optimising the conditions for the one-pot ethyl iodide deprotection and *in situ* cyclisation/hydrolysis sequence. It was immediately found that refluxing ethyl iodide **256** with activated zinc dust[100,101] in a solvent mixture of THF:0.1M acetic acid (9:1) resulted in the clean formation of the desired γ-lactone **258** in a very good yield of 89%. We were pleased to find that **258** was formed as a solid, and after slow evaporation in a solvent combination of hexane and DCM,

single crystals were formed and used for X-ray crystallographic analysis. It is evident from the X-ray crystal structure of **258** as shown in Figure 3-3, that the tricyclic core has the desired relative stereochemistries at C1, C4 and C9, confirming the stereochemical assignments given above.

Figure 3-3: X-ray crystal structure of **258**, the tricycle core of anislactones A/B



258

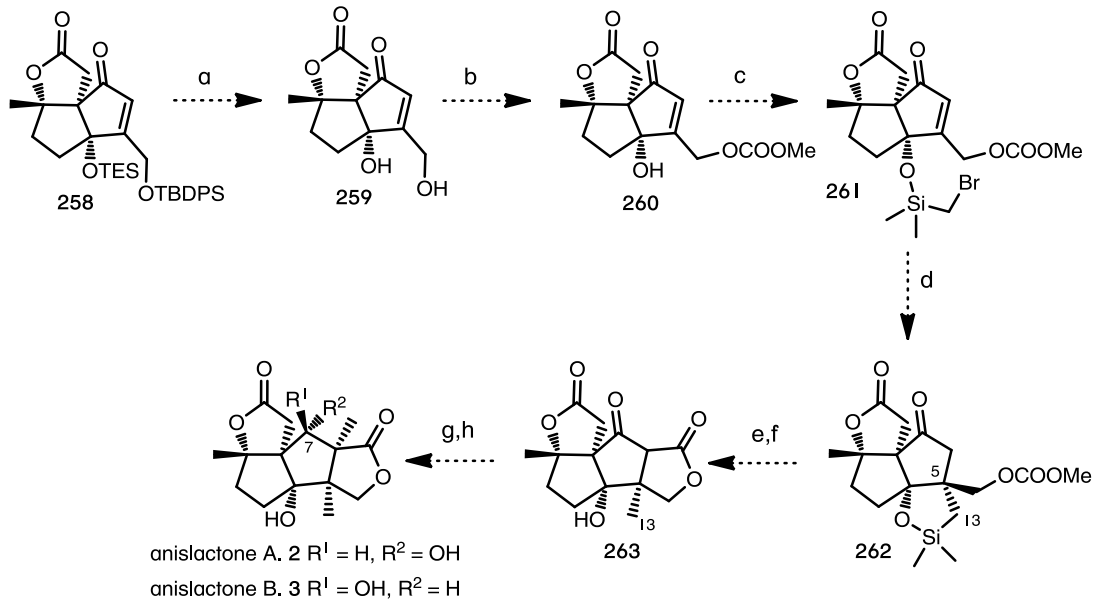
This represented a significant milestone in our synthesis as the tricyclic core of anislactones A/B had been accomplished in 13 synthetic steps. With three of the four rings of anislatones A/B now formed, **258** was then taken forward towards the next crucial transformation, a stereospecific Stork radical addition.[50]

3.5 Attempts at Formation of the C5 Quaternary Stereocentre

3.5.1 Stereospecific Stork silicon tethered radical addition

Having now secured the synthesis of the tricyclic core **258**, the next challenge was to introduce a methyl group stereospecifically forming the critical C5 quaternary stereocentre. We intended to perform a stereospecific Stork silicon-tethered radical addition to the enone and we envisioned the end-game strategy for the synthesis of anislactones A/B to proceed via a synthetic pathway as outlined in Scheme 3-10.[50]

Scheme 3-10: Envisioned synthetic sequence for Stork radical addition to enone and end-game strategy for anislactones A/B



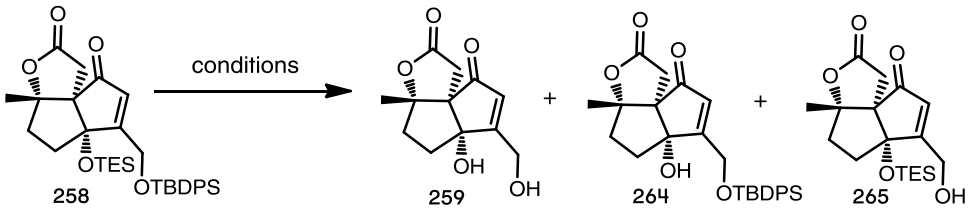
a) TBAF; b) ClCOOMe, NEt_3; c) $BrCH_2SiMe_2Cl$, NEt_3; d) Bu_3SnH, AIBN, PhH; e) NaH; f) TBAF; g) NaH, MeI; h) $NaBH_4$.

A global silyl deprotection of **258** was expected to proceed without difficulty followed by regioselective carbonate formation of the more sterically accessible primary alcohol to furnish **260**. Next, the silicon tether would be introduced by standard procedure, setting the stage for the stereospecific radical addition to the enone. The relatively low sensitivity of radical additions to steric hindrance was anticipated to facilitate, what would otherwise be, a very inaccessible Michael addition. Following this critical formation of the C5 quaternary stereocentre, the lactone could be built using well precedented alkylation chemistry.[102] A critical step is the fluoride-cleavage of the silicon tether to afford the C13 methyl group in **263**. This is a less common application of the silicon-tethered radical addition, but it has precedent in Stork's own research.[103] The methylation is expected to approach from the more accessible convex face followed by a reduction of the hindered ketone. As anislactones A/B are epimeric at C7 of the ketone then the diastereoselectivity of the reduction would

have little importance as it will likely lead to a successful total synthesis of at least one or both of anislactones A and B.

We expected the global silyl deprotection of **258** to be a straightforward transformation, but surprisingly we encountered a number of difficulties associated with substrate instability to basic reaction conditions and the formation of several unidentifiable side-products (Figure 3-4).

Figure 3-4: Screening of reaction conditions for silicon protecting group removal



Conditions	Result
TBAF, THF, RT, 24 hr	Substrate decomposition and side-products
5% HF:pyridine (7:3), THF, RT, 24 hr	**264**, **265** and side-products
AcOH:THF (1:1), TBAF (4 equiv), RT, 24 hr	No reaction
AcOH:THF (1:1), TBAF (4 equiv), reflux, 24 hr	SM, **264**, **265** and side-products
48% Aq HF:MeCN (1:6), 50 °C,	Substrate decomposition
0.5 M HCl, THF, RT, 24 hr	**264**, SM and unknown side-products
0.5 M HCl, THF, reflux, 2 hr	**264**, **265** and side-products
0.05 M HCl, THF, reflux, 7 hr	71% **264**

Initial efforts began with the standard TBAF silyl deprotection conditions which resulted in only substrate decomposition and significant amounts of unidentified by-products – none of the expected possible products **259**, **264** and **265**, were

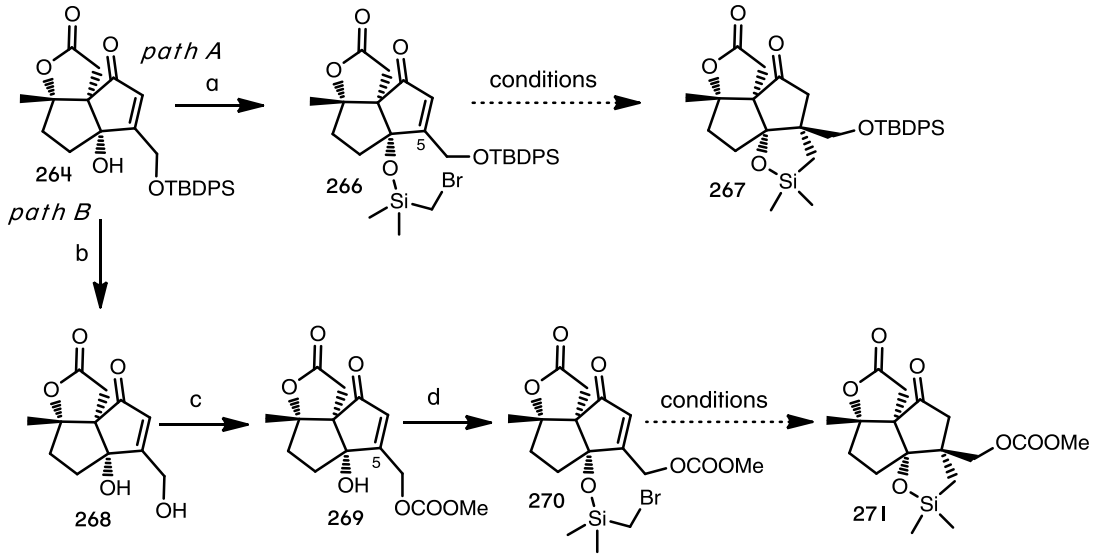
observed. Switching to 5% HF:pyridine resulted in less decomposition, but unfortunately a mixture of products remained and as seen previously, no formation of **259** could be seen. We envisaged better success with the use of TBAF buffered with AcOH,[58] but when conducted at room temperature, mostly starting materials remained. Elevating the temperature resulted in a mixture of products with significant quantities of starting materials left even after 24 hr and no formation of the desired **259** was detected.

These first set of observations made us turn our attention to acidic reaction conditions in the expectation that we would be able to selectivity remove the TES protecting group. Carrying out the reaction in THF with 0.5 M HCl led to the selective removal of the TES group leaving the TBDPS in place, but after 24 hr substantial quantities of by-products were observed together with unreacted starting materials. Elevating the reaction temperature led to the full consumption of starting materials but additional by-products were seen. However, this was encouraging, and finally refluxing **258** under less acidic conditions using 0.05 M HCL in THF over 7 hr, afforded TES deprotected **264** in a good 71% yield.

Having selectively uncapped the tertiary alcohol, we were now ready to install the required silicon tether. We chose to explore two possible paths, A and B, to the key intramolecular radical addition; the first being with the TBDPS group left in position; the second with a methyl carbonate in place of the TBDPS ether (Figure 3-5). Our incentive to remove the TBDPS ether was to reduce the steric congestion around the ß-carbon at C5 of the cyclopentenone, as this may adversely impact the ease at which the radical cyclisation proceeds. The substrates for the radical addition, **266** and **270**, were prepared via a set of relatively routine transformations. For **266** this included the capping of the free tertiary alcohol with the silicon tether whist carbonate **270** was obtained from **264** via a three step sequence of TBDPS deprotection under acidic HF:MeCN[104] conditions, carbonate formation and subsequent installation of the silicon tether. Attempts at the standard fluoride-

cleavage of the TBDPS group met with failure as only substrate decomposition was initially observed by TLC and LCMS analysis.

Figure 3-5: Attempts at the silicon tethered Stork radical addition on **266** and **270**



a) $BrCH_2SiMe_2Cl$, imidazole, DMAP, DCM, reflux, 95%; b) 48% Aq HF:MeCN (1:5), 50 °C, 89%;
c) ClCOOMe, NEt_3, DMAP, THF, reflux, 82%; d) $BrCH_2SiMe_2Cl$, imidazole, DMAP, DCM, reflux, 82%.

Conditions	Result: *Path A*	Result: *Path B*
Bu_3SnH (1.5 equiv), AIBN (0.2 equiv), degassed benzene, toluene or ^tBuOH, 80 °C, 0.004 M to 0.02 M under Argon, 24 hr	SM decomposition, unknown side-products	SM and unknown side-products
Bu_3SnH (1.5 equiv), AIBN (0.2 equiv, slow addition over 8 hr), degassed benzene or toluene, 80 °C, 0.02 M, under Argon, 24 hr	SM, unknown side-products	No reaction
Bu_3SnCl (0.2 equiv), $NaCNBH_3$ (2 equiv), AIBN (0.2 equiv), ^tBuOH, reflux	SM consumed, side-products	SM consumed, side-products
$(Bu_3Sn)_2$, sunlamp, benzene, 80 °C, 24 hr	SM and unknown side-product	SM and unknown side-products
Mg, I_2, THF, RT to 50 °C	Unknown side-products	Unknown side-products

Due to the highly advanced nature of these substrates, their availability was very limited and for that reason, the reactions were conducted on a very small scale ranging from 1 to 10 mg. Numerous attempts at the radical addition to the enone of both substrates **266** and **270** were conducted using the original conditions reported by Stork and colleagues.[50,103] Treatment of either substrate with AIBN, Bu_3SnH in one portion or slow addition over several hours and heated in a variety of solvents, led to substrate decomposition and unidentified side products. The isolation and purification of any products were complicated by the presence of tin-related byproducts, even after attempting to remove them by filtration following the common practice of a caesium fluoride workup.[105]

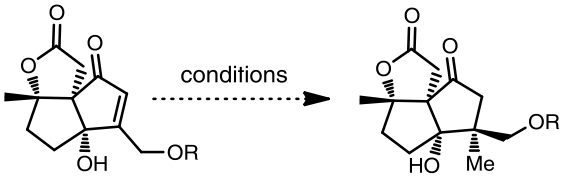
The side-products were difficult to identify by ^1H NMR due to presence of tin-related impurities that complicated the NMR spectrum. We did suspect that dehalogenation could be a competing reaction and thus, we investigated the *in situ* catalytic generation of Bu_3SnH using a procedure again developed by Stork.[103,106] The use of catalytic quantities of Bu_3SnCl in combination with $NaCNBH_3$ would result in the production of Bu_3SnH in low concentration. This has a number of benefits including a reduction of hydride transfer and thus dehalogenation, and a significant reduction in the amount of tin species making the purification process less problematic. To our disappointment, no such improvement was found and only unidentifiable side-products were detected by LCMS analysis. We attempted to avoid tin hydrides altogether by using bis(tributyltin) to produce the requisite tin radicals, but unfortunately after subsequent sunlamp irradiation similar unsatisfactory results were obtained. Finally, we investigated the formation of a Grignard from the alkyl bromide of the silicon tether which was expected to immediately perform a stereospecific conjugate addition to the enone. This reaction consumed starting materials, but afforded just byproducts that were unable to be identified.

At this stage, the Stork radical addition was abandoned and our next aim was to find a path forward using the remaining limited quantities of advanced intermediate **264**.

3.5.2 1,4-Conjugate additions to Anislactone A/B tricyclic core

A common method for the introduction of substituents to the ß-carbon of enone-type systems is the Michael addition. This has widespread use as a classic C–C bond forming reaction in organic synthesis and is able to generate tertiary and quaternary stereocentres. There are a variety of reagents that are commonly used in such transformations such as Grignard, dialkylzinc, organolithium, trialkylaluminium reagents and organocuprate species such as Gilman's reagent.[107-110] We decided to investigate the prospect of introducing the methyl substituent via a conjugate-type reaction, expecting the nucleophile to approach selectively from the more accessible *exo*-face due to either sterics or because of the potential directing effect of the tertiary alcohol at C4. There is literature precedent for the alcohol-directed *syn*-addition of Grignards[111,112] and trialklyaluminiums[113-115] to structurally similar cyclopentenone substrates. As shown below in Figure 3-6, we performed an extensive screen of reagents and reaction conditions for the 1,4-addition of a methyl nucleophile to three advanced intermediates, enones **264**, **268** and **269.**

Figure 3-6: Attempts at methyl 1,4-conjugate addition to enones **264**, **268** and **269**



R = TBDPS **264**
R = OH **268**
R = COOMe **269**

R = OH **272**
R = TBDPS **273**
R = COOMe **274**

Entry	Conditions	Result
1	MeMgBr, THF or Et_2O, RT or reflux	No reaction
2	MeMgBr, $BF_3{\cdot}Et_2O$, THF or Et_2O, RT to reflux	No reaction
3	MeMgBr, CuI or $CuBrSMe_2$, THF or Et_2O, RT to reflux	No reaction
4	$AlMe_3$, toluene, –78 °C to RT,	No reaction
5	$AlMe_3$, $Ni(acac)_2$ or $Cu(OTf)_2$, toluene or THF, –78 °C to RT,	No reaction
6	$Zn(Me)_2$, $Ni(acac)_2$ or $Cu(OTf)_2$, THF, Et_2O or toluene	No reaction
7	MeLi, CuI, THF or Et_2O, –78 °C to RT,	SM consumed and complex mixture
8	Me_2CuLi, THF or Et_2O, –78 °C or –45 °C to RT	No reaction; decomposition at higher temperature (–45 °C)

Our attempts began with methylmagnesium bromide, hoping that an intramolecular chelation-directed delivery of the Grignard species to the ß-carbon of enones **264**, **268** and **269** would yield the desired products.[112] Unexpectedly, we observed no reaction with only starting materials left untouched, even after adding an excess of

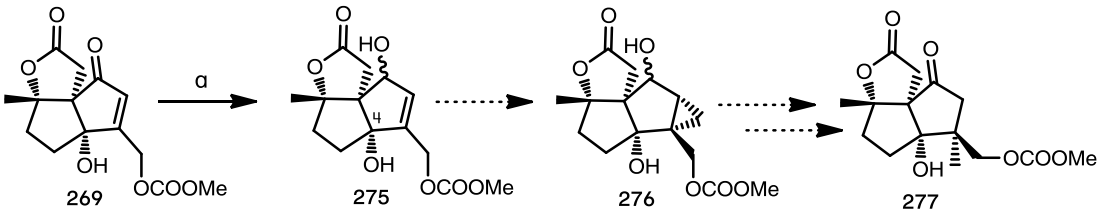
Grignard and elevating the temperature (entry 1). The addition of Lewis acid or copper salts did not lead to any improvement with unreacted starting materials again left behind (entries 2 and 3). Use of trimethylaluminium was investigated next on its own or with catalysts, $Ni(acac)_2$[116] or $Cu(OTf)_2$,[117,118] and we were met with the same disappointment with no conversion of starting materials, even when treated with an excess of trimethylaluminum (entries 4 and 5). Organozinc derivatives are typically less reactive but additionally have a tendency to add in a conjugate fashion to α,ß-unsaturated carbonyl compounds in contrast to their relative inertness towards saturated ketones. However, when dimethylzinc was employed together with $Ni(acac)_2$[119-122] or $Cu(OTf)_2$,[123] only starting materials were identified in the reaction mixture by TLC and LCMS analysis (entry 6). Consequently, we made the decision to examine the use of more reactive alkylating reagents such as methyllithium and Gilman's reagent, which was prepared from methyllithium and copper iodide.[124] For the first time we observed the consumption of starting materials with both methyllithium and Me_2CuLi. With methyllithium in the presence of a catalytic amount of CuI at –78 °C, we detected only starting materials but ambient temperatures resulted in the instant formation of a complex mixture (entry 7). Similarly, treatment with Me_2CuLi offered no improvement at –78 °C and a slight increase in the temperature to -45 °C resulted in immediate decomposition of the substrate (entry 8).

In summary, we were quite astounded at the stability of the three substrates to Grignard, organoaluminium and organozinc reagents, even at elevated temperatures. This could be reasoned by the extreme steric congestion at the fully substituted C5 carbon, particularly in the case of **264**, which has the bulky TBDPS group as an element capable of blocking the approach of any nucleophile.

3.5.3 Attempts at alcohol-directed cyclopropanation

As a last effort in progressing carbonate **269** through the synthesis, we examined the possibility of a diastereoselective cyclopropanation using the alcohol at C4 as a directing group.[125,126] First, a Luche reduction of carbonate **269** was required to provide a suitable substrate for the cyclopropanation on the isolated trisubstituted alkene (Scheme 3-11). The reduction was preferred to be *syn*-diastereoselective with respect to the C4 alcohol but unfortunately, we were not able to ascertain the relative stereochemistry of the single diastereomer **275**, even with extensive NOESY analysis. In the event that the following cyclopropanation successfully afforded the desired diastereomer **276**, we anticipated that a simple oxidation of the secondary alcohol, followed by a regioselective cleavage of the cyclopropyl bond by a samarium iodide-induced single electron transfer reaction would selectively furnish **277**.[127] The regioselective cyclopropyl bond cleavage was expected because of the inherent stability of the formed ketyl radical intermediate.[128]

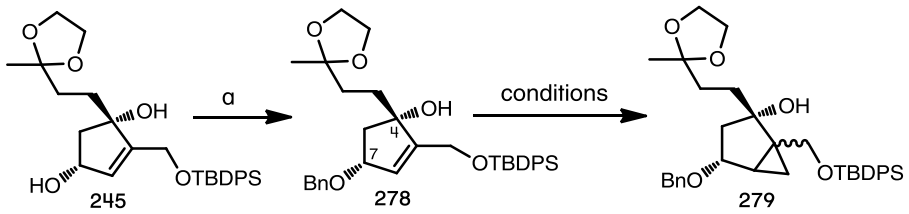
Scheme 3-11: Directed cyclopropanation approach to the formation of the C5 quaternary stereocentre



a) $NaBH_4$, $CeCl_3.7H_2O$, 0 °C, 64 %, single diastereomer.

There were limited amounts of **269** available and therefore, we decided to develop the cyclopropanation conditions on an earlier intermediate **245** for which we had an ample quantity for the optimisation process. Benzyl protection of the secondary alcohol of **245** went smoothly, furnishing the desired substrate **278** for the cyclopropanation in a respectable 63% yield. We were able to assign the relative stereochemistries at C4 and C7 because of the absence of any nOe interactions between the benzyl ether at C7 and the dioxolane side-chain at C4 (Figure 3-7).

Figure 3-7: Cyclopropanation model system



a) BnBr, Bu_4NI, NaH, THF, RT, 63%.

Entry	Conditions	Result
1	Zn-Cu,[129] CH_2I_2, Et_2O, reflux	25% yield[a]
2	Et_2Zn, CH_2I_2, Et_2O, DCM or DME/DCM, 0 °C to RT	18% yield[b]
3	$Si(CH_3)_3CHN_2$, CuI, or CuCl, Et_2O or toluene, RT	SM and by-products
4	Sm, $HgCl_2$, CH_2I_2, THF, –78 °C to RT	SM, traces of product and decomposition
5	Sm, CH_2I_2, THF, RT	No reaction

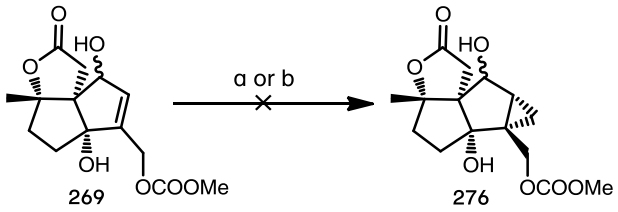
[a] **Method A** was used in the synthesis; [b] **Method B** was used in the synthesis.

We first explored the well-known Simmons–Smith method for cyclopropanation. One of the most important features of the Simmons-Smith reaction is its ability to use functional groups containing heteroatoms to direct the cyclopropanation from the face of the double bond having closer proximity to the functional group.[130] In our system, there are two possible functional groups that can exert a directing effect, the C4 alcohol and the C7 benzyl ether. The original conditions of Simmons–Smith were employed and a single diastereomer of the desired product **279** was furnished in a poor 25% yield. Applying the Furukawa modification[131,132] using diethylzinc did not offer any improvement, furnishing the same **279** in 18% yield (entry 2). Upon increasing the amounts of the diethylzinc, no further rise in the yield was observed. The use of the diazomethane equivalent, trimethylsilyldiazomethane (entry 3),

samarium metal with mercuric chloride[128] (Molander modification,[133] entry 4) and samarium in diiodomethane[134] (entry 5) resulted, at best, in the detection of trace amounts of product as identified by LCMS. The stereochemistry of cyclopropane **279** could not be determined as the 2D-NOESY spectrum proved inconclusive but we hoped if successful, the NOESY data of tetracycle **276** would be more decisive.

The supply of the starting material **245** was depleted after this initial screen and even though the yield was not as desirable as we hoped, we nevertheless decided to apply the conditions developed above to our late-stage intermediate, carbonate **269** (Scheme 3-12).

Scheme 3-12: Attempt at a late-stage alcohol-directed cyclopropanation



a) Zn-Cu,[129] CH_2I_2, Et_2O, reflux; b) Et_2Zn, CH_2I_2, Et_2O, 0 °C to RT.

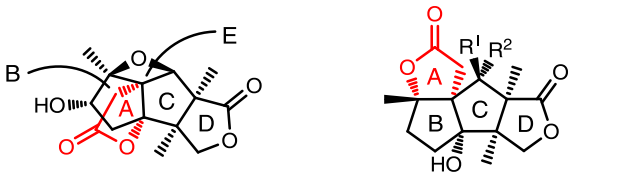
We were met with disappointment as both the conditions of Simmons-Smith and Furukawa were fruitless, with no desired product detected by TLC or LCMS analysis and only unreacted starting materials remained. This outcome combined with the previous attempts at installing the angular methyl at C5 represented a major setback to our planned synthesis of anislactones A/B. With three of the four carbocycles of anislactones A/B completed, it was very frustrating that we encountered so many difficulties in establishing the C5 quaternary stereocentre. The lack of success in the attempts at diastereoselective conjugate addition and cyclopropanation reactions are perhaps not altogether surprising given the extreme steric congestion around the fully substituted ß-carbon of the enone. This was the main driving force behind the intramolecular stereospecific Stork radical addition approach which after much experimentation was in our hands unsuccessful.

It was at this juncture that we decided a modification to the original synthetic route was necessary. This new retrosynthesis would still employ the efficient intramolecular cyano-aldol reaction, but would incorporate a new strategy for the installation of the two angular methyls, creating the C5 and C6 quaternary stereocentres. The next chapter shall be concerned with the development of this new synthetic strategy, employing a different approach to the anislactone carbon skeleton.

3.6 Synthesis of the Tricyclic ABC Core of Merrilactone A

Anislactones A/B and merrilactone A are structurally related as demonstrated by Fukuyama during the successful chemical conversion of anislactone B to merrilactone A via a simple three-step synthetic sequence (cf. Section I.5). Additionally, the Greaney group syntheses of merrilactone A and anislactone A showed that both natural products could be accessed through a regiodivergent approach from a common intermediate.[25] Careful inspection of the carbon frameworks reveals that the ABC tricyclic core for both merrilactone A and anislactones A/B differ only in the position of the A-ring lactone as highlighted in Figure 3-8. In merrilactone A, the A-ring lactone forms a ring junction with the C-ring in contrast to the B ring in anislactones A/B.

Figure 3-8: Position of the lactone A-ring in anislactones A/B and merrilactone A

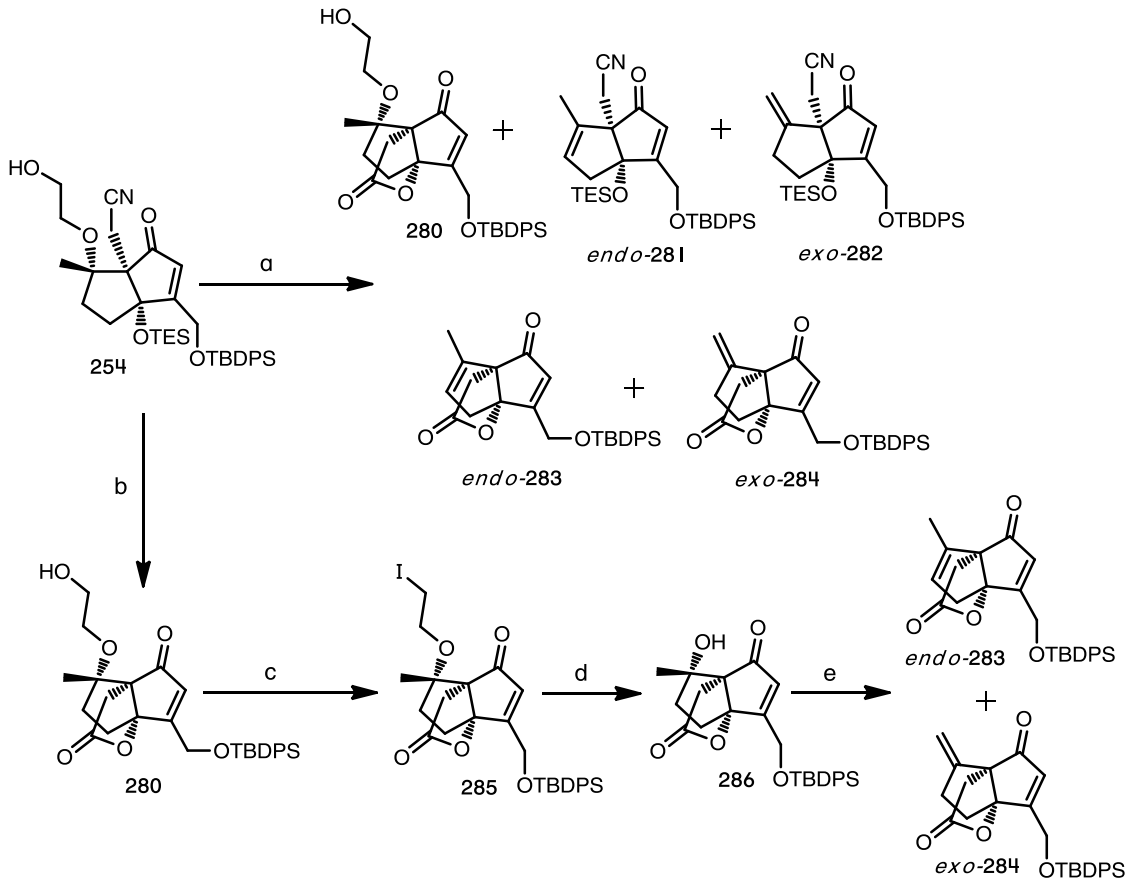


After our effort towards anislactones A/B had come to a temporary halt, we explored an opportunity to access the tricyclic core of merrilactone A. The cyano-aldol product **254** contains the full carbon skeleton of both ABC tricyclic cores of the natural products, enabling a divergent approach to both natural products by regioselective formation of the A-ring lactone. We have already successfully demonstrated the synthesis of the anislactone tricyclic core, which then led us to focus our attention on tackling merrilactone A. It was anticipated that a selective TES ether deprotection of **254** could undergo *in situ* cyclisation/hydrolysis, forming the desired A-ring lactone in a one-pot reaction. If this proved unfeasible, then a step-wise synthesis of the lactone via a carboxylic methyl ester would be carried out.

Our previous experiences with selective silyl deprotections led us to consider the Lewis acid $BF_3{\cdot}Et_2O$ as a possible selective reagent.[135]

Subsequent exposure of bicycle **254** with excess $BF_3{\cdot}Et_2O$ in DCM at RT led to the formation of tricycle **280** in a good 68% yield (Scheme 3-13). We reasoned that a trace amount of water in the $BF_3{\cdot}Et_2O$ was sufficient to hydrolyse the imidate intermediate *in situ*. It was evident from the TLC that other side-products were formed and subsequent LCMS analysis of the crude reaction mixture led to the unexpected detection of trace amounts of *endo*-bicycle **281**, *exo*-bicycle **282**, *endo*-tricycle **283** and *exo*-tricycle **284**.

Scheme 3-13: Synthesis of tricyclic core of merrilactone A via either a one-pot multi step system or a linear step-wise synthetic sequence

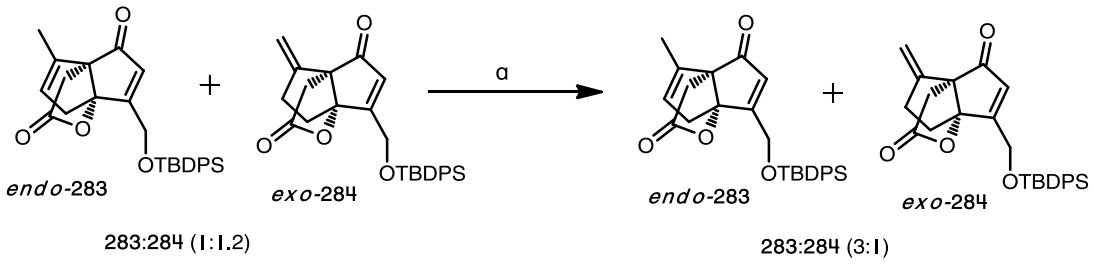


a) **Method B:** $BF_3{\cdot}Et_2O$, DCM, reflux, 13 % **280**, 19% *endo*-**281** and *exo*-**282**, 1:1.5, 7% *endo*-**283** and *exo*-***284*** (1:0.6), 7% recovered **254**; b) **Method A:** $BF_3{\cdot}Et_2O$, DCM, 30 °C, 68%; c) I_2, PPh_3, imidazole, DCM, RT, 73%; d) Zn dust, THF:0.1 M AcOH (9:1), reflux, 65 % yield; e) Burgess reagent, DCM, reflux, *endo*-***283*** and *exo*-***284***, 76%, 1:1.2 mixture of regioisomers.

This is an astonishing result and our initial thought was that with careful manipulation of the reaction conditions, we could alter the direction of the reaction towards the selective formation of the desired *endo*-tricycle **283**. If successful, this would represent a one-pot multi-step system incorporating a selective TES deprotection, *in situ* cyclisation followed by subsequent hydrolysis, and selective ethane-diol elimination. Using the same procedure but under refluxing conditions in DCM, we were able to isolate **280** (13% yield), a 1:1.5 regioisomeric inseparable mixture of *endo*-**281** and *exo*-**282** (19% combined yield), a 1:0.6 inseparable mixture of regioisomers *endo*-**283** and *exo*-**284** (7% combined yield), and recovered starting materials **254** (7% yield). Attempts at more forcing conditions, such as elevated temperatures in toluene, resulted in an increasingly complex mixture together with the gradual removal of the TBDPS group. Although we were not able to achieve a selective and efficient synthesis of *endo*-**283**, it did however demonstrate that the core of merrilactone A could be synthesised in a very respectable 12 synthetic steps via the common intermediate **254**.

Next, we wanted to establish the step-wise conversion of common intermediate **254** into the desired merrilactone A core **283**. Continuing from lactone **280**, a conversion of the primary alcohol to an iodide went smoothly, affording ethyliodide **285** in a good 73% yield. The well-rehearsed reductive cleavage of **285** provided tertiary alcohol **286** which, after *syn*-elimination of the alcohol using Burgess[136] reagent, furnished an inseparable 1:1.2 mixture of double bond regioisomers *endo*-**283** and *exo*-**284**, in a combined yield of 76%. Finally, we attempted the isomerisation of *exo*-**284** by treatment with *p*-TsOH·H_2O in refluxing benzene. Although this increased the regioisomeric ratio from 1:1.2 to 3:1 (*endo*-**283***:exo*-**284**) this was achieved in a disappointing 23% yield (Scheme 3-14). The reaction was monitored by LCMS and from the analysis of these data we were able to attribute the poor yield to the instability of the TBDPS group under the refluxing acidic conditions.

Scheme 3-14: Double bond isomerisation of an inseparable diastereomeric mixture of *endo*-**283** and *exo*-**284**



a) *p*-TsOH, benzene, reflux, 23% *endo*-**283**:*exo*-**284** (3:1).

Further elaboration of **283** was not possible because of the limited supply of advanced material and knowing that we may have faced similar difficulties to those previously encountered enroute to anislactones A/B. Additionally, we needed to factor sufficient research time for our proposed modified synthetic route to both natural products. Even so, we have now successfully demonstrated that the tricyclic cores of anislactones A/B and merrilactone A can be accessed via a common intermediate. Furthermore, we discovered an unexpected one-pot reaction of the common BC ring intermediate **254** to the tricyclic ABC core **283** which would otherwise require several linear synthetic transformations if conducted in a step-wise manner. NMR spectra for select compounds along both the anislactone A/B and merrilactone A routes are presented in the appendix.

4 Formal Synthesis of Merrilactone A and the Carbon Skeleton of Anislactones A/B

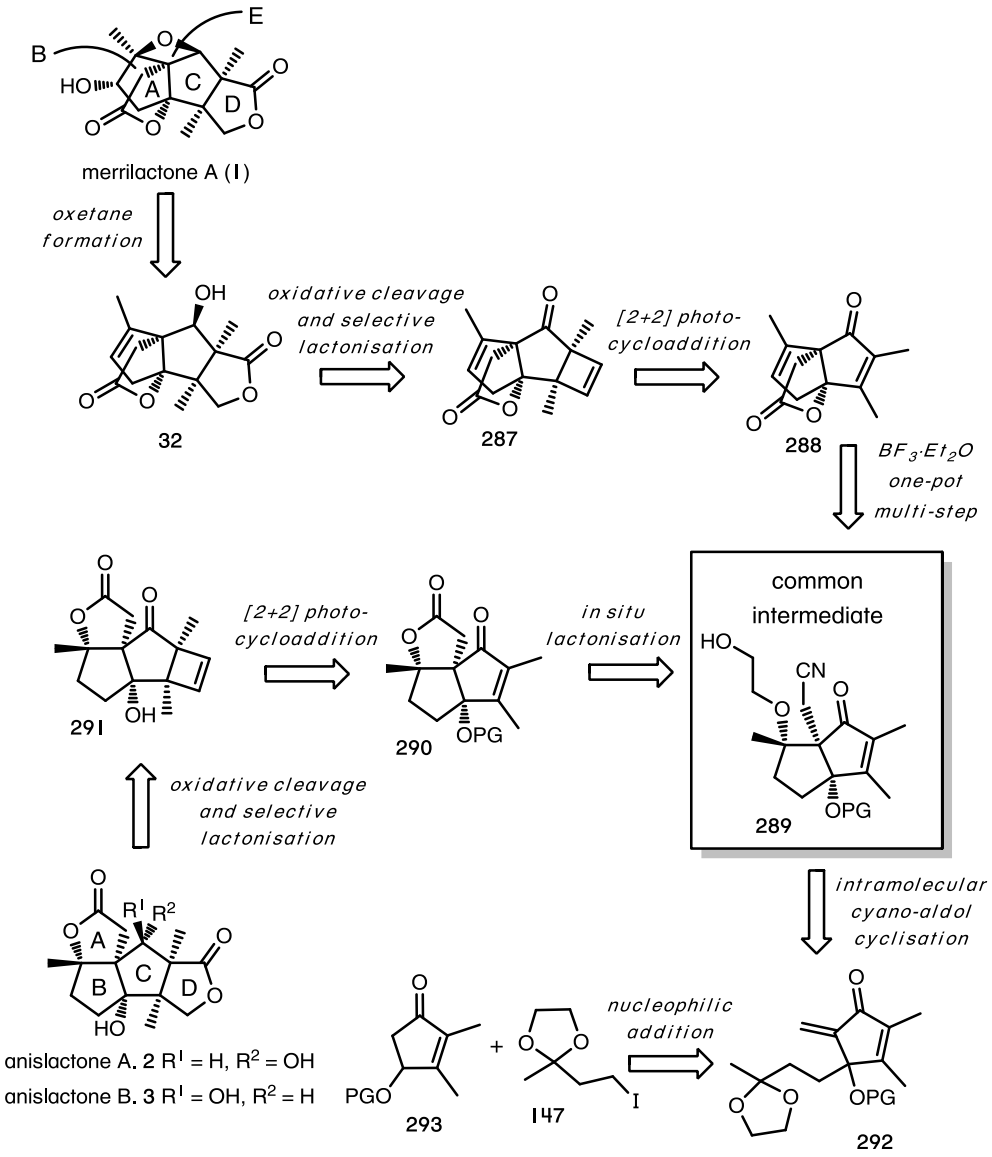
A modification to our synthetic plans was required to advance our research. It was the introduction of the C5 quaternary stereocentre that had halted our progress, and we endeavoured to first address this challenge. The successful cyano-aldol cyclisation reaction was to remain a key part of the newly proposed synthetic route which meant that any changes would have to be compatible with this transformation. We decided upon incorporating a [2+2] photocycloaddition, adapted from Mehta's synthesis of merrilactone A,[22] as a possible method for the late-stage introduction of both C5 and C6 quaternary stereocentres. Such an approach would be amenable to the synthesis of both sets of natural products, but it would it would undoubtedly require the synthesis of different starting materials.

4.1 Retrosynthetic Analysis

In our proposed retrosynthesis, we envisaged the BC intermediate from the product of the key cyano-aldol cyclisation **289** would enable regiodivergent synthesis of both anislactone A/B and merrilactone A (Scheme 4-1). Bicycle **289** has the complete carbon framework of the tricyclic ABC cores of both sets of natural products and could be directed to either via orthogonal lactonisation sequences. Beginning with merrilactone A (**1**), we expect the well-established two-step sequence transformation of **32** to merrilactone A via stereoselective epoxidation and subsequent *homo*-Payne rearrangement to proceed without difficulty.[17,23] The substrate for this two-step sequence would be available from selective lactonisation and oxidative cleavage of cyclobutene **287** installing the γ-lactone D ring. Next, a crucial diastereoselective late-stage [2+2] photocycloaddition of tricycle **288** with dichloroethylene was envisaged to give the desired diastereomer. This represents the most significant change to our previous approaches and has literature

precedence on structurally related substrates in Mehta's synthesis of merrilactone A and related model studies.[22,26] The tricyclic substrate **288** for this reaction would in turn be available from the previously developed Lewis acid treatment of BC common intermediate **289**. If unsuccessful, a feasible backup would be a stepwise sequence of transformations. In a similar fashion, anislactones A/B could be obtained from cyclobutene **291** via oxidative cleavage and selective lactonisation. Cyclobutene **291** would in turn be accessed by a [2+2] photocycloaddition of tricycle **290**, which is hoped to be selective for the required diastereomer **291**. The installation of the γ-lactone A-ring was then envisioned to be achieved by the familiar procedure of zinc-mediated reductive cleavage and *in situ* lactonisation of BC intermediate **289**. The key intramolecular cyano-aldol cyclisation reaction of *exo*-methylene **292** would provide BC bicycle **289**, which represents the common intermediate used for the regiodivergent synthesis of both natural products. The substrate for the cyano-aldol cyclisation would itself be prepared from the 1,2-nucleophilic addition between iododioxolane **147** and dimethylcyclopentenone **293**, an easily prepared literature compound.[137]

Scheme 4-1: Retrosynthetic analysis for the regiodivergent approach to merrilactone A and anislactones A/B

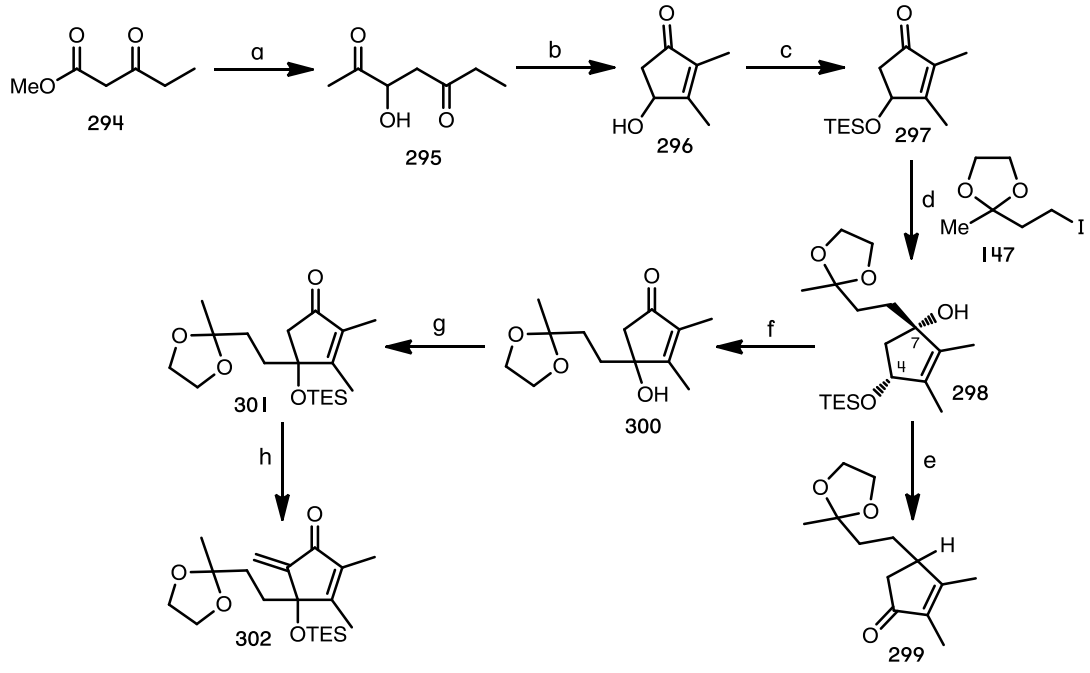


4.2 Synthesis of the Cyano-Aldol Cyclisation Substrate

In our new strategy towards both anislactones A/B and merrilactone A, we had to synthesise new starting materials. Fortunately, the desired dimethylcyclopentenone **293** is a literature compound prepared via a straightforward two-step synthesis.[137] Thus, treatment of **294** with aqueous KOH for six days, followed by bubbling carbon dioxide and the addition of pyruvaldehyde into the reaction afforded 1,4-diketone

295 in moderate yield (Scheme 4-2). Addition of potassium carbonate to a solution of diketone **295** in MeOH whilst ensuring the internal temperature did not exceed 8 °C, successfully afforded the desired dimethylcyclopentenone in a good 72% yield. Subsequently, a routine TES ether formation followed by organolithium addition of the prepared iodoacetal **147** cleanly furnished tertiary alcohol **298** as a single diastereomer. The bulky TES ether group at the C4 stereocentre efficiently controlled the facial selectivity of the organolithium addition, transferring stereochemistry to C7. The assigned stereochemistry is a result of extensive NOESY analysis that revealed key nOe signal enhancements between CH at C4 and the introduced ketal side chain. The absence of any nOe interactions between the TES group at C4 and the ketal supported the stereochemical assignments assigned below.

Scheme 4-2: Synthesis of the key cyano-aldol cyclisation substrate **302**



a) KOH, H_2O, CO_2, 4 °C to RT, then pyruvaldehyde 58%; b) K_2CO_3, MeOH, 0 °C to RT, 72%; c) TESCl, NEt_3. DMAP, RT, 89%; d) **147**, ^tBuLi, Et_2O, –78 °C, 86%; e) TCNQ, THF:H_2O (9:1), RT, 51%; f)) TBAF, DCM, RT, then TPAP, NMO, RT, 93%; g) TESOTf, 2,6-lutidine, DMF, RT, 91%; h) i) LDA, $[CH_2{=}NMe_2]^+ I^-$, THF, –78 °C to RT; ii) *m*CPBA, DCM:$NaHCO_3$ (2:1), RT, 65% (two steps).

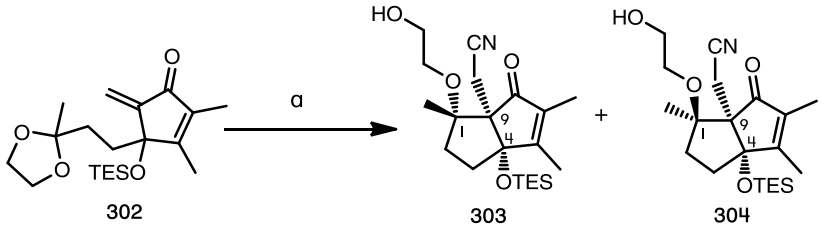
We first attempted a TCNQ cleavage of the TES ether, a procedure successfully used on a structurally related substrate (cf. Scheme 2-5). Unexpectedly, we did not detect any desired product but instead were able to isolate an intriguing by-product in 51% yield which we characterised to be enone **299**. This surprising outcome seems to be a result of a number of different transformations including silyl deprotection, oxidation and reduction in the same step. We were not able to propose a reasonable mechanism but this reaction would perhaps warrant further investigation. Switching to the one-pot reaction of standard fluoride-cleavage of the TES group and immediate TPAP oxidation yielded tertiary alcohol **300** in an excellent 93% yield over two steps. Finally, TES protection of the hindered tertiary alcohol **300** and subsequent methylenation using Eschenmoser's salt and consecutive *m*CPBA elimination, furnished the cyano-aldol substrate **302** in a yield of 65% over two steps.

Pleasingly, we were thus able to demonstrate the viability of the new synthetic route using different starting materials in the synthesis of *exo*-methylene **302**, a suitable substrate for the upcoming crucial cyano-aldol cyclisation.

4.3 Intramolecular Cyano-Aldol Cyclisation Reaction

With the stage now set for the key cyano-aldol reaction, we were pleased to discover that treatment of 1,1-disubstituted alkene **302** with diethylaluminium cyanide followed by $TiCl_4$ at –20 °C successfully afforded a separable 7:1 mixture of diastereomers **303** and **304** in a 70% combined yield (Scheme 4-3). Our previous experiences with the cyano-aldol reaction (cf. Section 3.3) meant that we expected major diastereomer **303** to have the desired relative stereochemistry at the newly formed triad of stereocentres C1, C4 and C9.

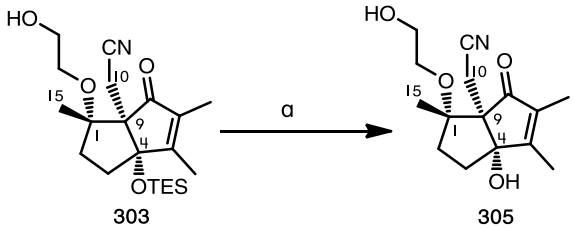
Scheme 4-3: Key intramolecular tandem cyano-aldol cyclisation reaction



a) Et_2AlCN, $TiCl_4$, toluene, 0 °C, 70% combined, 62% **303**, 8% **304**, d.r. 7:1.

X-ray crystallography proved unfeasible, as diastereomers **303** and **304** were both formed as oils. To confirm our predictions, we attempted to determine the relative stereochemistry of both diastereomers by means of extensive 1D and 2D-NMR spectroscopy. Using 1D-^{1}H-NMR, ^{13}C-NMR, and DEPT, as well as COSY, HSQC and HMBC 2D correlation spectroscopy allowed us to assign all the proton and carbon signals observed. Unfortunately, analysis of the NOESY spectrum was inconclusive and thus, we were not able at this stage to assign the relative stereochemistry of both diastereomers (the stereochemical assignments represented in Scheme 4-3 were confirmed at a later stage and are assigned retrospectively). Nevertheless, we were fortunate that the fluoride-cleavage of the TES ether of major diastereomer **303** led to diol **305** as a solid (Scheme 4-4).

Scheme 4-4: Formation of a single crystal of **305** for X-ray analysis

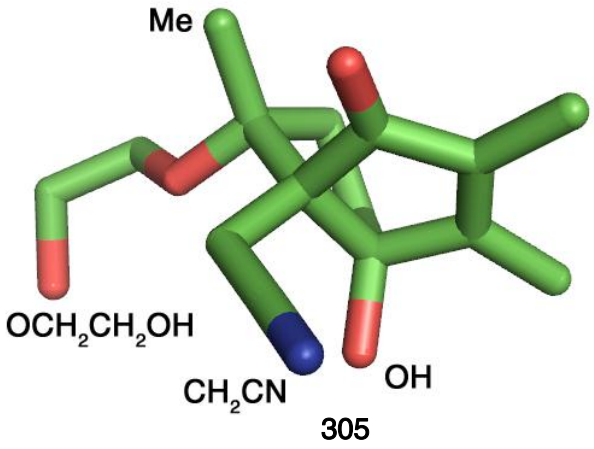


a) TBAF, THF, RT, 82%.

This allowed us to obtain a single crystal for X-ray crystallographic analysis that would provide the absolute proof of its stereochemistry and its progenitor **303** (Figure 4-1). As highlighted in the crystal structure, the important C15 methyl and C10 CH_2CN substituents have the desired *anti* stereochemical relationship, which is

in agreement with our predictions and the previous stereochemical assignments of diastereomers **303** and **304.**

Figure 4-1: X-ray crystal structure of TES deprotected cyano-aldol product **305**



305

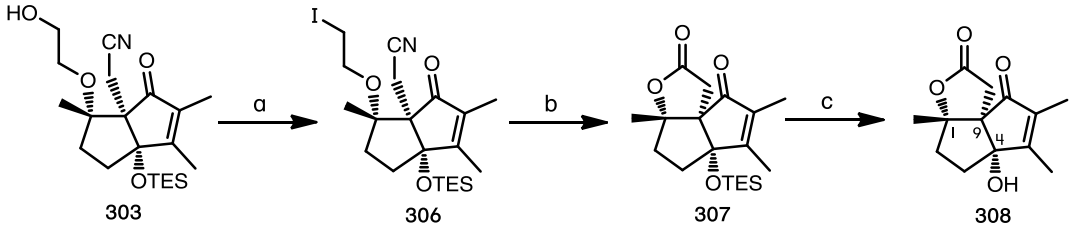
4.4 Synthesis of the Carbon Framework of Anislactones A/B

4.4.1 [2+2] Photocycloaddition

With the key cyano-aldol cyclisation reaction now established, we began to move towards the crucial [2+2] photocycloaddition. We first employed the previously developed methodology to obtain the tricyclic substrate **307** for the cycloaddition (cf. Section 3.4). Opening with the cyano-aldol product **303**, we were able to simply obtain ethyl iodide **306** which was then subjected to zinc-mediated reductive cleavage conditions (Scheme 4-5). This resulted in the same pot, clean deprotection of the ethyliodide, *in situ* cyclisation and subsequent hydrolysis, yielding the anislactone tricyclic core **307** in a very good 87% yield. Without the possibility of complications observed for diprotected **258** (cf. Figure 3-4), TBAF treatment of tricycle **307** cleanly removed the TES group yielding **308** containing the fully established stereocentres at C1, C4 and C9. With the substrate **307** for the crucial photocycloaddition in hand, we proceeded to examine the potential of this [2+2]

cyclisation reaction in the hope that the TES group would impart the necessary steric hindrance resulting in the desired facial selectivity for the cycloaddition.

Scheme 4-5: Synthesis of key [2+2] photocycloaddition substrate **307**



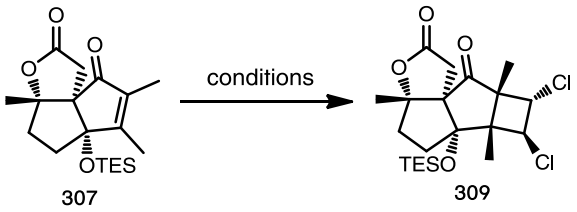
a) I_2, PPh_3, imidazole, DCM, RT, 94%; b) Zn dust, THF:0.1 M AcOH (79:1), reflux, 87%; c) TBAF, THF, RT, 97%.

Our first attempts were based on methodology published in Mehta's synthesis of merrilactone A, but exact details of the conditions employed were not available from the available supporting information.[22] A medium-pressure mercury vapour lamp was used as the initial irradiation light source. The spectral output of mercury arc lamps ranges from 254 nm to 580 nm with multiple peak wavelengths at 365 nm, 405 nm and 436 nm. A Pyrex filter was first employed which only allows radiation of wavelengths of 280 nm or longer to pass through and thus cuts off high-energy short-wavelength radiation.

We then screened a variety of conditions including solvent and light filter as summarised in Figure 4-2. Unfortunately in our hands, the combination of a Pyrex filter and a variety of solvents led to mostly full recovery of starting materials even after 72 hr of irradiation (entry 1). Traces of product were detected by LCMS with concurrent formation of significant amounts of TES-deprotected byproducts. Increasing the substrate concentration by seven-fold and using *trans*-dichloroethylene as the solvent provided no improvement even over similar time lengths (entries 2 and 3). Due to mostly starting materials being recovered and only a minor conversion to product as detected by LCMS, we decided to investigate the influence of wavelength of light employed. Immediate success came in the form of a

Rayonet photochemical reactor equipped with 254 nm bulbs (6 × 10 W) and a quartz filter. With just four hours of irradiation in cyclohexane, we successfully obtained tetracyclic **309** in a fair 42% yield, but was complicated by some unwanted reduction byproducts of the enone (entry 4). This marked improvement was attributed to the full transmission of high-energy 254 nm light, which would be mostly cut-off in the case of a Pyrex filter. We discovered optimal conditions to be neat *trans*-dichloroethylene at a substrate concentration of 0.07 mM, which significantly reduced the amount of reduction by-products and furnished tetracyclic **309** as a clean single diastereomer in a reasonable 44% yield (entry 5). In this transformation we installed both angular methyls at C5 and C6 in a *syn*-fashion, forming two quaternary stereocentres in a single step.

Figure 4-2: Key [2+2] photocycloaddition approach to the full carbon framework of anislactones A/B

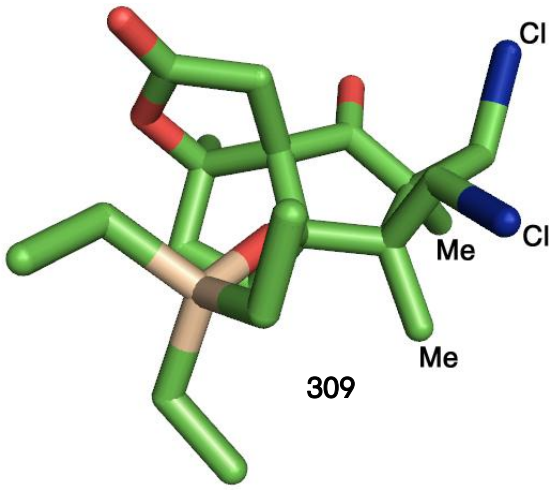


Entry	Conditions	Irradiation Source	Filter	Time (hr)	Result
1	*trans*-dichloroethylene 50 to 250 equiv, acetone/MeCN/cyclohexane, [substrate] = 0.014 mM, RT	Medium-pressure Hg vapour lamp	Pyrex	72	SM remaining, TES deprotection, traces of product
2	*trans*-dichloroethylene 50 to 250 equiv, cyclohexane, [substrate] = 0.1 mM	Medium-pressure Hg vapour lamp	Pyrex	72	SM remaining, TES deprotection, traces of product
3	neat *trans*-dichloroethylene, [substrate] = 0.014 mM	Medium-pressure Hg vapour lamp	Pyrex	54	SM remaining, TES deprotection, traces of product
4	*trans*-dichloroethylene 50 equiv, cyclohexane, [substrate] = 0.014 mM, RT	Rayonet photochemical reactor, 254 nm	quartz	4	42 % and possible reduction product
5	neat *trans*-dichloroethylene, [substrate] = 0.07 mM, RT	Rayonet photochemical reactor, 254 nm	quartz	4	44 %

The relative stereochemistry of cycloadduct **309** could not be confidently established by the full suite of NMR spectroscopic techniques, including 2D-NOESY analysis. Nevertheless, **309** was furnished as a white solid, which after slow evaporation in hexane and DCM, yielded single crystals suitable for X-ray analysis. The outcome of the X-ray crystallographic analysis confirmed cycloadduct **309** to be the undesired diastereomer with the *trans*-dichloroethylene predominantly approaching from the α-face (Figure 4-3). This was unexpected as it was rationalised that the bulky TES

protecting group would impart enough steric congestion to provide at least some ß-facial selectivity in the approach of dichloroethylene.

Figure 4-3: X-ray structure of photocycloaddition product **309**



309

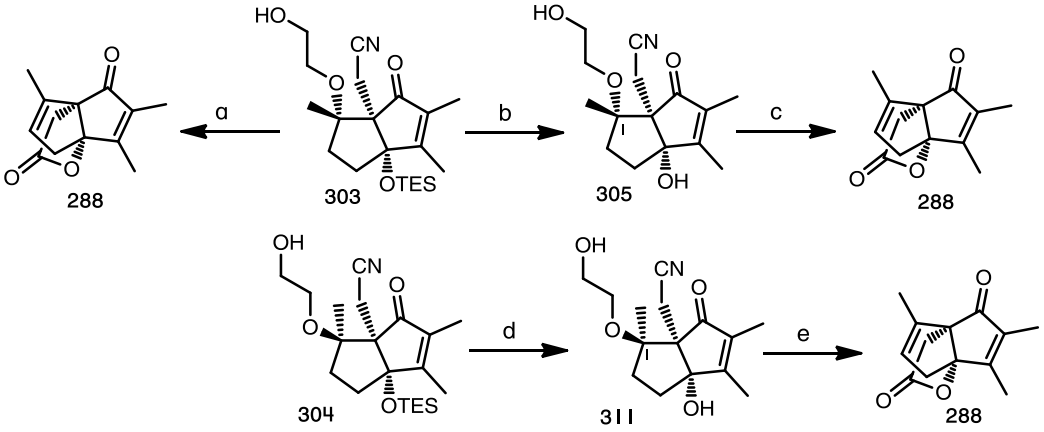
At this juncture, we had to abandon our approach to anislactones A/B and focus the limited amount of remaining research time towards the synthesis of merilactone A. We would have liked to have more time to explore the scope of this cycloaddition on other analogues of **307**, but unfortunately this was not possible.

4.5 Formal Total Synthesis of Merrilactone A

4.5.1 Lewis acid mediated one-pot multi-step reaction

After ending our pursuit of anislactones A/B, we turned our attention immediately to the synthesis of merrilactone A. We anticipated the $BF_3{\cdot}Et_2O$ multi-step reaction would likely be more efficient as cyano-aldol product **303** lacks the TBDPS group that was previously shown to be labile at elevated temperatures in the presence of $BF_3{\cdot}Et_2O$ (cf. Section 3.6). Gratifyingly, exposure of **303** with $BF_3{\cdot}Et_2O$ in toluene at 75 °C furnished the desired *endo*-tricycle **288** with the installed γ-lactone A-ring as a single double bond regioisomer in a 35% yield (Scheme 4-6). This marked a significant step forward, as the original reaction delivered an inseparable regioisomeric mixture of *endo- and exo*-tricycles **283** and **284** in very poor yield (cf. Section 3.6). There was obvious room for improvement and, thus we were interested if an analogue such as **305**, without the TES protecting group, would be a more suitable substrate. A straightforward fluoride induced silyl deprotection provided tertiary alcohol **305**, which was subsequently treated with the Lewis acid, $BF_3{\cdot}Et_2O$.

Scheme 4-6: Lewis acid assisted one-pot reaction for the synthesis of the tricyclic ABC core of merrilactone A

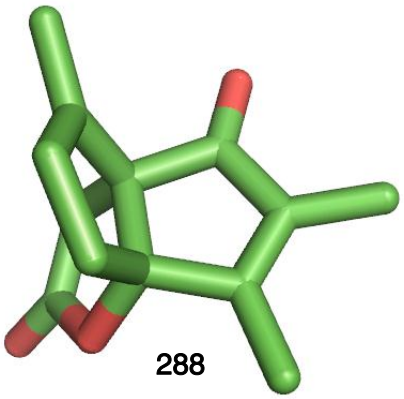


a) **Method A:** $BF_3{\cdot}Et_2O$, toluene, 75 °C, 35%; b) TBAF, THF, RT, 82%; c) **Method B:** $BF_3{\cdot}Et_2O$, toluene, 100 °C, 86%; d) TBAF, THF, RT, 82%; e) $BF_3{\cdot}Et_2O$, toluene, 100 °C, 82%.

To our complete satisfaction, *endo*-**288** was afforded as a single double bond regioisomer in a very good 86% yield. We were fortunate to obtain *endo*-**288** as a solid, from which X-ray analysis unambiguously confirmed its structure (Figure 4-4).

This represents a highly efficient one-pot multi-step transformation that would otherwise have required a linear series of up to *six* synthetic steps. Additionally, we demonstrated that because the C1 stereochemistry is destroyed and replaced by an sp^2 carbon centre, we could also funnel through the remaining minor diastereomer product **304** of the cyano-aldol reaction. In a similar fashion as before, *endo*-**288** was thus obtained with comparable yields.

Figure 4-4: X-ray structure of the key tricyclic ABC core **288** of merrilactone A



288

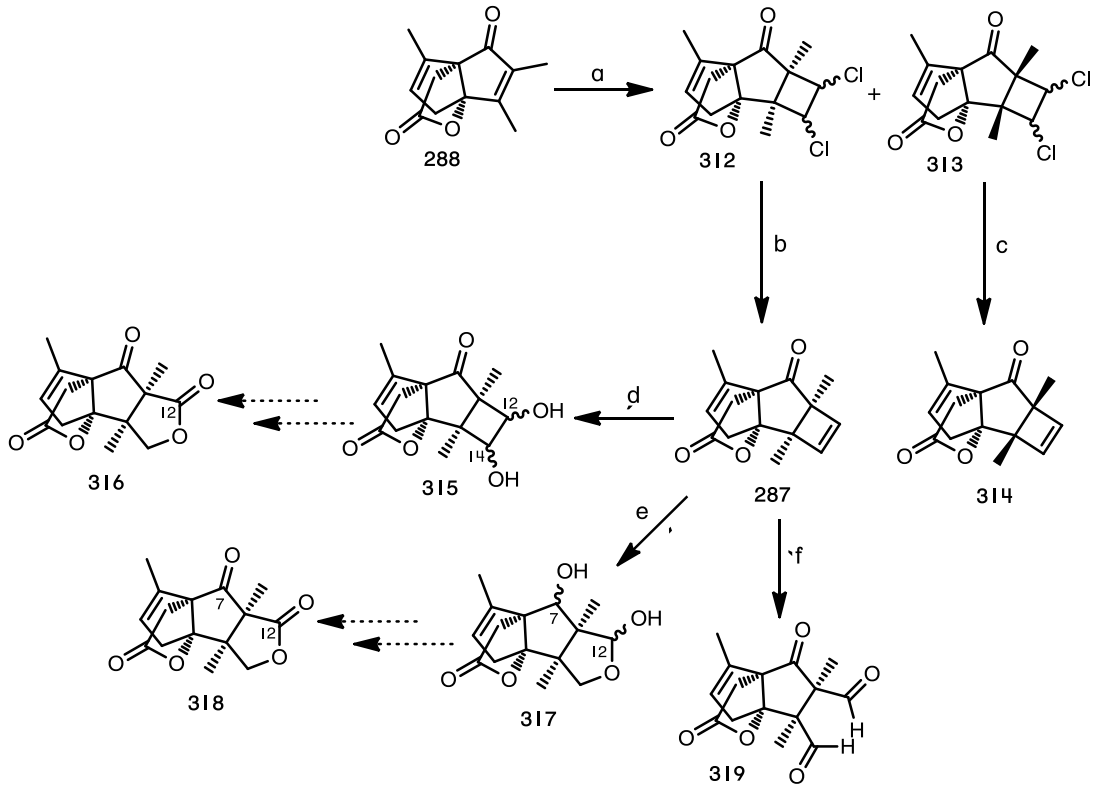
We have now achieved the synthesis of the tricyclic core of merilactone A core in a relatively short 11 synthetic steps via both diastereomeric products of the key cyano-aldol cyclisation reaction.

4.5.2 [2+2] Photocycloaddition

With tricycle **288** in hand, we next turned our attention to the installation of the γ-lactone D-ring and quaternisation of the two vicinal methyl groups. We adopted the same method of [2+2] photocyclisation conditions used in the synthesis of the tetracyclic core of anislactones A/B (cf. Section 4.4.1). However, this time our substrate is more representative of the compound used in Mehta's synthesis and we

expected to observe a similar diastereoselectivity. On our first attempt, the irradiation of **288** proceeded with moderate degree of β-facial selectivity leading to the formation of a 2:1 mixture of diastereomers in favour of tetracyclic **312** and in a reasonable combined yield of 60% (Scheme 4-7).

Scheme 4-7: End-game strategy for the formal total synthesis of merrilactone A



a) neat *trans*-1,2-dichloroethylene, *hν* (254 nm, quartz), RT, 41% **312**, 19% **313**, d.r. 2:1; b) Zn dust, Ac_2O, TMSCl, toluene, 100 °C, 73%; c) Zn dust, Ac_2O, TMSCl, toluene, 100 °C, 74%; d) OsO_4 (4 mol%), NMO, ± pyridine Acetone:H_2O, RT; e) i) O_3, DCM:MeOH (9:1), –78 °C; ii) $NaBH_4$, –78 °C to RT; f) i) O_3, DCM:MeOH (9:1), –78 °C; ii) Me_2S, –78 °C to RT.

Although the cyclobutanes **312** and **313** were prepared successfully, no crystalline forms could be obtained for X-ray crystallographic analysis. Since confirmation of the structures of **312** and **313** was thus not possible *via* crystallographic methods, we turned our attention to 2D-NMR spectroscopy. Unfortunately, it was not possible to completely assign the stereochemistry of either diastereomer, even with extensive analysis of the NOESY spectrum. The assignments given in Scheme 4-7 are based

on the elucidation of stereochemistry at a later stage *(vide infra)* and were assigned retrospectively.

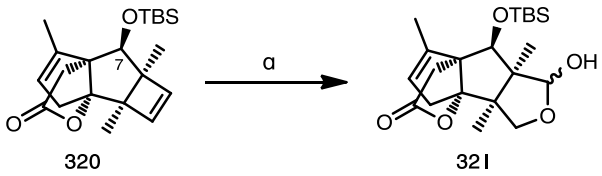
The zinc-mediated eliminative dechlorination[21] of either **312** or **313**, turned out to be more problematic than expected, but eventually with the use of a large excess of activated zinc in toluene, we were able to obtain cyclobutenes **287** and **314** in 73% and 74% yield, respectively. Again we were not able to assign the relative stereochemistry for either cyclobutene. For the moment, we assumed the major diastereomer had the desired relative stereochemistry and thus, moved forward through the synthesis with **287**. The next challenge was the regioselective formation of the γ-lactone D-ring from the chemically equivalent cyclobutene ring. Our first approach was to attempt an OsO_4 induced regioselective dihydroxylation[138] of the cyclobutene ring. This was rationalised because of the lower reactivity and the steric encumbrance around the trisubstituted alkene of the B ring. It was envisaged after a $NaIO_4$-mediated cleavage and reduction of the resultant dialdehyde, that the ensuing diol could be selectively oxidised to the desired γ-lactone **316**. The regioselective oxidation of the C12 alcohol using Fetizon's reagent[139] has literature precedence in both Hirama's and Greaney's own synthesis of merrilactone A (cf. Scheme 1-12).[19,25] Thus, exposing **287** to catalytic OsO_4, stoichiometric NMO and excess pyridine[138,140] only resulted in a slow conversion to **315** with a lesser amount of the *bis*-dihydroxylation product. After leaving for 48 hr at room temperature, no further conversion was observed with only traces of product detected by LCMS. Elevating the temperature or increasing the catalytic loading of OsO_4 resulted in more of the unwanted double dihydroxylation of both alkenes and less of **315**.

With this disappointment, we decided to investigate the prospect of ozonolysis as another means of selectively cleaving the cyclobutene ring. We initially adopted the general conditions used by Mehta[22] and following treatment of **287** with ozone at –78 °C, the solution turned a pale blue colour indicating the full consumption of starting materials which was additionally confirmed by TLC. A

subsequent reductive $NaBH_4$ workup yielded only a complex mixture from which no desirable product could be isolated or detected by TLC or LCMS. An attempt at the oxidation of both C7 and C12 alcohols via a successive PDC oxidation of the crude mixture to **318** provided no improvement. Likewise, the option of forming the dialdehyde **319** by way of quenching with dimethyl sulfide was examined but this again proved to be fruitless.

We suspected that in addition to the cyclobutene, the trisubstituted alkene was also reactive towards ozone which would offer an explanation for the observed complex mixtures. This was somewhat surprising as in Mehta's synthesis of merilactone A, the ozonolysis of the cyclobutene **320** proceeded without difficulty affording lactol **321** in 45% yield over two steps (Scheme 4-8).[22]

Scheme 4-8: Regioselective lactonisation in Mehta's synthesis of merrilactone A



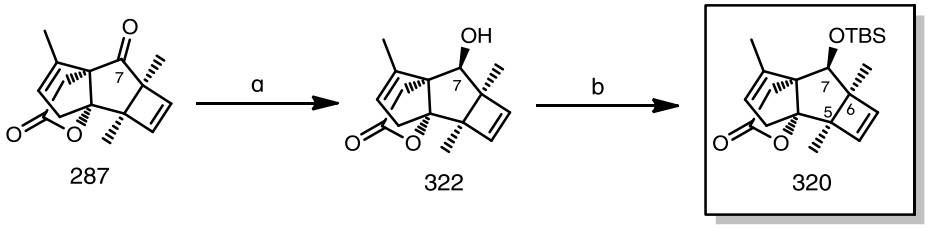
a) i). O_3, MeOH, –78 °C; ii). $NaBH_4$, MeOH, –78 °C, 45% (two steps).

Our substrate is similar but not identical, and it could be reasoned that the bulky TBS ether at C7 of **320** provided the necessary steric congestion to block any direct approach of ozone to the trisubstituted alkene.

At this point in our research, the availability of advanced intermediates was extremely limited and so we chose to halt all attempts at forming the γ-lactone D ring. Instead, we focussed on completing a formal total synthesis of merrilactone A via a known intermediate in Mehta's synthesis (Scheme 4-9).[22] Reduction of the C7 ketone with $NaBH_4$ delivered hydride from the more accessible α-face, affording **322** as a single diastereomer in a very good 81% yield. Protection of the newly formed tertiary alcohol as a TBS ether required the highly reactive reagent TBSOTf, due to the extreme sterically congested environment around C7. Even so, it was essential

for the reaction to be left for five days before the reaction was predominantly complete, furnishing Mehta's advanced intermediate **320** in 81% yield. Tetracycle **320** represents the entire carbon skeleton of merilactone A, featuring all the required functionalisation to advance it to the natural product as previously been demonstrated by Mehta and colleagues.[22]

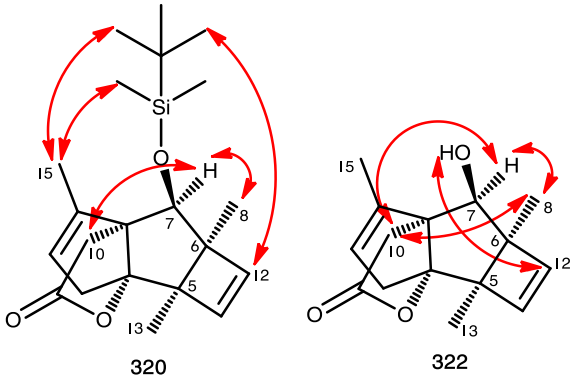
Scheme 4-9: End-game sequence for the formal total synthesis of merrilactone A



a) $NaBH_4$, MeOH, RT, 81%; b) TBSOTf, NEt_3, DCM, 30 °C, 81%.

An X-ray crystal structure of tetracycle **320** would have been the definitive proof of its stereochemistry but it formed only as a clear viscous oil from which no solids could be obtained. Our attention then turned towards the use of extensive 1D and 2D-NMR spectroscopic methods. We were able to assign all observed proton and carbon signals via advanced COSY, DEPT, HSQC and HMBC NMR experiments. This allowed us to identify the key nOe interactions in the NOESY spectrum, enabling us to determine its structure and relative stereochemistry. Additionally, we analysed the spectroscopic data for its precursor, tertiary alcohol **322** to substantiate our stereochemical claims for both **322** and **320** (Figure 4-5).

Figure 4-5: nOe signals observed for **322** and known intermediate **320**



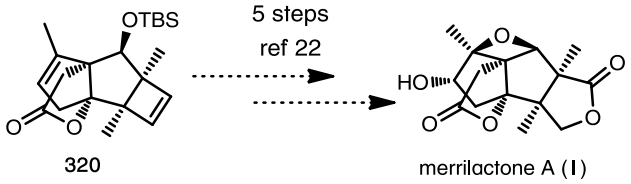
The defining stereochemical configuration was the orientation of the secondary alcohol in **322** and the TBS ether in **320**. If we could demonstrate their location to be on the ß-face and opposite to the methyl substituents at C8 and C13, we would be able to confirm the stereoselectivity of two key reactions, the [2+2] photocycloaddition of **288** and the facial selectivity of the $NaBH_4$ reduction of ketone **287**. Strong correlation peaks were observed between the C8 methyl and the single proton at C7, for both **320** and **322**. Additionally, nOe interactions were seen for the proton at C7 and the C10 methylene protons, and the methyl substituents of the TBS group to both the C15 methyl and alkene proton at C12. These observations combined with the comparison of both NOESY data sets, proved that the $NaBH_4$ delivered the hydride selectively from the α-face of **287**. In addition, this also strongly suggested that the C8 and C13 methyl substituents are positioned on α-face confirming moderate ß-facial selectivity during the photocycloaddition. These observed specific nOe interactions provided the proof for the stereochemical assignments given above and previous retrospective assignments.

With the characterisation data for Mehta's intermediate **320** freely available, we were also able to perform a direct comparison of the signals detected in the ^{1}H- and ^{13}C-NMR spectra. We were pleased to find a perfect alignment of our proton and carbon signals to those reported.[22] However, an anomaly in Mehta's ^{1}H-NMR data was discovered; the single proton at C7 was absent, but unfortunately we could

not inspect the original ^{1}H-NMR spectrum to confirm this as a copy of the original spectrum was not provided in the supporting information. Nevertheless, we are convinced that our stereochemical assignments are correct and that we successfully synthesised **322**, which represents a racemic formal synthesis of merrilactone A.

In Mehta's own synthesis of merrilactone A, known intermediate **320** could be converted to merrilactone A via a five-step synthetic sequence (Scheme 4-10). We therefore achieved the formal synthesis of merrilactone A in 15 synthetic steps (20 steps to merrilactone A) with an overall yield of 2%. NMR characterisation spectra for the compounds along this route are presented in the appendix.

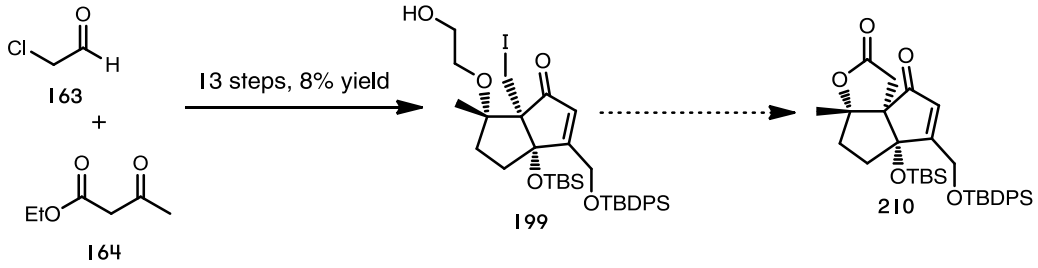
Scheme 4-10: Synthesis of merrilactone A from known intermediate **320**



5 Conclusions

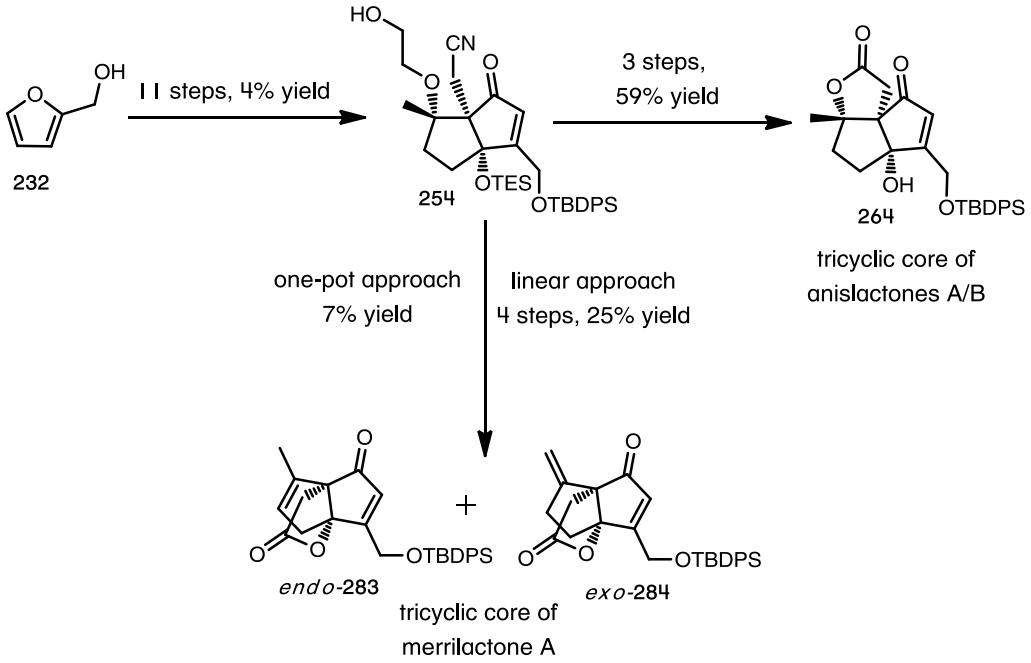
In our initial work on the intramolecular iodo-aldol cyclisation reaction (cf. Section 2.3), we successfully synthesised the BC bicyclic core of the anislactones and demonstrated that this one-pot reaction could be used for the synthesis of carbocycles containing *vicinal* quaternary and tertiary stereocentres (Scheme 5-1).

Scheme 5-1: The intramolecular iodo-aldol cyclisation approach



Although the synthesis of bicycle **199** was achieved, attempts at further elaboration and installation of the γ-lactone A-ring was met repeatedly with disappointment. We then focused our attention on the development of a new synthetic route incorporating a MBH reaction for a more efficient synthesis of starting materials (cf. Section 3.1) and replaced the iodo-aldol reaction with a novel cyano-aldol cyclisation reaction (cf. Section 3.3). The intramolecular cyano-aldol cyclisation reaction proved to be a success and enabled a regiodivergent synthesis of the tricyclic cores of anislactones A/B and merrilactone A (Scheme 5-2).

Scheme 5-2: Regiodivergent approach to the tricyclic cores of anislactones A/B and merrilactone A via a novel intramolecular cyano-aldol cyclisation reaction



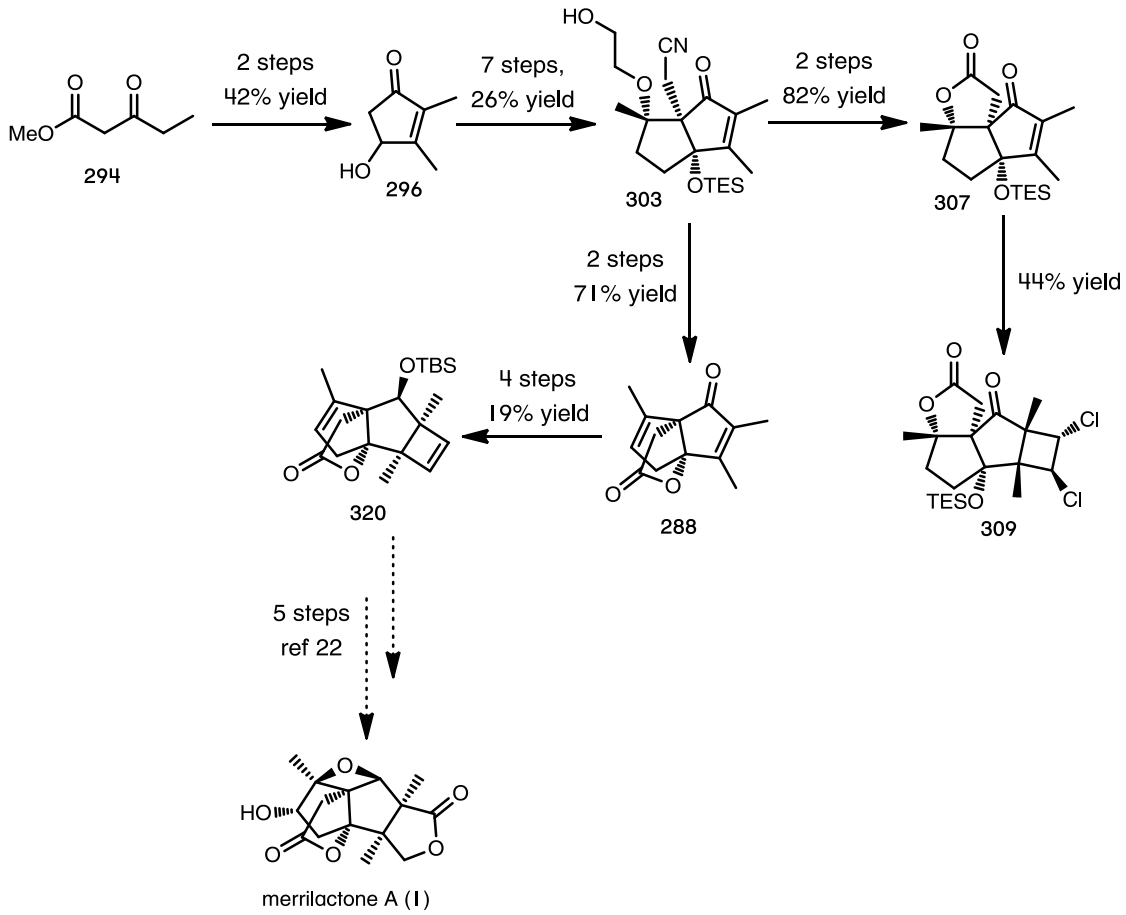
The absence of any tandem cyano-aldol reactions in the literature and its successful application in this research for the synthesis of complex fused-ring structures makes this transformation even more exciting. Additionally, whilst developing the route to the merrilactone A core, we discovered an unexpected transformation during a routine silyl deprotection of cyano-aldol product **254** using the Lewis acid, $BF_3{\cdot}Et_2O$. We were able to access the tricyclic core of merrilactone A via a linear sequence of synthetic transformations from **254**, but found that simple treatment with $BF_3{\cdot}Et_2O$ at slightly elevated temperatures furnished in one-pot, the tricyclic cores *endo*-**283** and *exo*-**284**, albeit in a very low 7% combined yield. Although the yield is of concern, the number of transformations taking place in this one-pot reaction is nevertheless impressive.

We were disappointed to find that further advancement of both tricyclic cores of anislactones A/B and merrilactone A were not possible. The proposed Stork silicon-tethered radical addition (cf. Section 3.5.1) and numerous attempts at a methyl 1,4-conjugate addition were ultimately fruitless (cf. Scheme 3.5.2). This came

as a major setback as we had to abandon and make modifications to the originally planned synthetic route. This new strategy involved a late-stage [2+2] photocycloaddition that was expected to lead to the γ-lactone D-ring via a chemically equivalent cyclobutene. New starting materials were chosen to be amenable to the three key reactions, [2+2] photocycloaddition, cyano-aldol reaction and the one-pot Lewis acid mediated *in situ* lactonisation and elimination reaction.

Entry to this new approach was gained from commerically available methyl propionylacetate **294** that was used in the literature preparation of the desired dimethyl-cyclopentenone **296** (Scheme 5-3). The cyano-aldol cyclisation product **303** was synthesised from dimethylcyclopentenone **296** via a secondary alcohol protection, 1,2-nucleophilic addition, one-pot TES deprotection/oxidation, and methylenation. Cyano-aldol product **303** was used as the common intermediate for the regiodivergent synthesis of anislactones A/B and merrilactone A. Starting with anislactones A/B, the γ-lactone A-ring was introduced via a one-pot reductive ethyliodide deprotection and *in situ* lactonisation, affording the tricyclic core **307**. This was used as the substrate for the key [2+2] photocycloaddition and cyclobutene **309** was isolated as the only diastereomer. Unfortunately, **309** has the undesired stereochemistry at the newly formed quaternary stereocentres at C5 and C6, confirmed by an X-ray crystal structure. This was a major disappointment, and consequently, we had to abandon our approach for the synthesis of anislactones A/B and instead concentrated our efforts on merrilactone A.

Scheme 5-3: A regiodivergent approach to the total formal synthesis of merrilactone A and the tetracyclic core of anislactones A/B



Synthesis towards merrilactone A began with the silyl deprotection of common intermediate **303** furnishing the substrate for the one-pot $BF_3{\cdot}Et_2O$ induced reaction, which proceeded smoothly to afford **288**, the tricyclic core of merrilactone A. In this one-pot reaction, multiple transformations had taken place including *in situ* cyclisation/hydrolysis and regioselective elimination of the ethane-diol side-chain. An interesting aspect of this reaction is the selective formation of the *endo* double bond in **288** as this negates the need for a separate alkene isomerisation step, common to most of the published total syntheses of merrilactone A.[17,23,25] Finally, the [2+2] photocycloaddition represents a crucial C–C bond forming reaction that pleasingly afforded the desired cyclobutene with the required stereochemistry, albeit with low levels of stereoselectivity. Subsequent selective $NaBH_4$ reduction and TBS protection of the extremely hindered secondary alcohol led to the synthesis of the

known intermediate **320** in Mehta's synthesis of merrilactone A.[22] Confirmation of the stereochemistry of **320** was obtained via extensive 2D-NOESY analysis and the comparison with NOESY data of **322**. The exact match of the proton and carbon NMR signals of **320** to those published by Mehta[22] substantiated the stereochemical assignments and our claim of a successful synthesis of **320**.

This signified a 15 synthetic step sequence to the formal total synthesis of merrilactone A and 20 steps to the natural product. The synthesis describes a direct approach to the BC bicyclic core **303** via the first novel demonstration of a diastereoselective cyano-aldol cyclisation as the defining transformation. A manuscript summarising the research presented in this thesis is currently in preparation.

6 Experimental Procedures

6.1 General Procedures

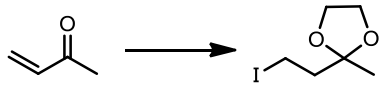
NMR spectra were recorded at ambient temperature on a Brüker AVA600 (600 MHz), Brüker AVA500 (500 MHz), Brüker DPX360 (360 MHz) and Brüker AC250 (250 MHz) instruments and calibrated to residual solvent peaks: ^{1}H – $CDCl_3$, 7.26 ppm and ^{13}C – $CDCl_3$, 77.0 ppm. The ^{1}H-NMR data are presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet), coupling constant (J in Hz) and structural assignment. The ^{13}C-NMR data are reported in ppm on the δ scale, followed by the structural assignment, based on DEPT spectra. The single X-ray crystallographic data were collected via Single Crystal X-Ray Diffraction (SXRD) using an Agilent Technologies SuperNova instrument equipped with a Gemini Source and Atlas detector. IR spectra were recorded on a JASCO FT/IR-4160 Plus instrument, using 4 mm sodium chloride or KBr discs and wavelengths of the maximum absorbance (ν max) are quoted in cm^{-1}. High-resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using LTQ Orbitrap XL, Finnigan MAT 95XP and Finnigan MAT 900XLT instruments for FAB, ESI and ASA analysis. The data are presented as the ionisation method, followed by the calculated and measured masses. Elemental composition results were provided by NRM laboratories Ltd and the data are quoted as the % w/w. TLC was performed on Merck 60 F254 silica plates and visualised by UV light and/or anisaldehyde[§] or

[§] Anisaldehyde stain was prepared by carefully adding concentrated sulfuric acid (10 mL) to a stirred ethanol solution (200 mL) of *p*-methoxybenzaldehyde (10 mL).

potassium permanganate[**] stain. Compound purification was carried out by wet flash column chromatography, using Merck Kieselgel 60 (particle size 35-70) under positive pressure. Eluent constitution is quoted as ratios or percentages. Solvents were dried before use unless otherwise stated. Anhydrous solvents were obtained from a solvent purification system supplied by www.glasscontour.com or a PureSolv solvent purification system supplied by Innovative Technologies Inc. All other chemicals were purchased from a chemical supplier and used as received. Experiments were performed under an inert atmosphere of nitrogen gas under anhydrous conditions using oven dried glassware unless otherwise stated. Photoreactions were carried out in either a photoreactor supplied by Photochemical Experimental Reactors Ltd., Reading, UK, using a 400 W medium pressure mercury vapour lamp under a N_2 atmosphere and water cooling, or a Rayonet photochemical reactor supplied by Southern New England Ultraviolet Company, Connecticut, USA, equipped with 254 nm bulbs (6 × 10 W).

[**] Potassium permanganate stain was prepared by dissolving potassium permanganate (3 g) and potassium carbonate (20 g) in sodium hydroxide (5%, 5 mL) and H_2O (300 mL).

2-(2-Iodoethyl)-2-methyl[1,3]dioxolane **147**



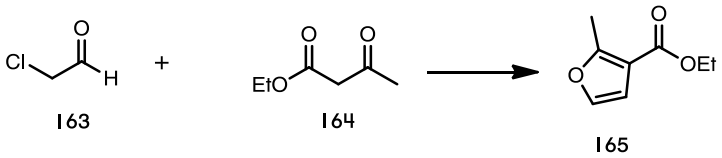
179 **147**

A solution of sodium iodide (51.3 g, 0.34 mol, 1.2 equiv) and 3-buten-2-one **179** (20 g, 0.29 mol, 1 equiv) in anhydrous acetonitrile (350 mL) was vigorously stirred whilst rapidly adding chlorotrimethylsilane (37.2 g, 0.34 mol, 1.2 equiv). This generated a suspension that was left stirring for 25 mins at which time a solution of ethylene glycol (21.3 g, 0.34 mol, 1.2 equiv) was added rapidly and the mixture was stirred for a further 25 mins. The reaction mixture was then poured onto 5% $NaHCO_3$ (100 mL)overlaid with hexane (400 mL). This produced three distinct layers, the bottom layer being the aqueous, the middle acetonitrile and top layer hexane. The bottom aqueous layer was removed and the remaining organic phases were washed with 5% sodium thiosulfate ($Na_2S_2O_3$, 1 x 100 mL). The aqueous extracts were combined and extracted twice with EtOAc (400 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* with the water bath set to less than 25 °C to prevent decomposition. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished dioxolane **147** as a colourless oil (33.7 g, 49% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 – 3.86 (m, 4H, OCH_2CH_2O), 3.20 – 3.13 (m, 2H, ICH_2CH_2), 2.34 – 2.26 (m, 2H, ICH_2CH_2), 1.31 (s, 3H, CH_3C); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 110.0 (q), 65.0 (CH_2), 44.4 (CH_2), 23.9 (CH_3), -2.2 (CH_2).

The spectroscopic data were in agreement with those previously published.[62]

2-Methylfuran-3-carboxylic acid ethyl ester **165**



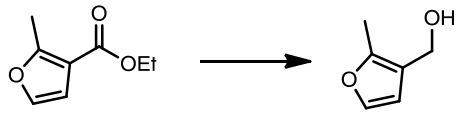
163 **164** **165**

A mixture of ethyl acetoacetate **164** (300 g, 2.30 mol, 1 equiv) and pyridine (547 g, 6.92 mol, 3 equiv) was stirred on ice, while a solution of 45% aqueous chloroacetaldehyde **163** (362 g, 4.61 mol, 2 equiv) was slowly added over a period of 30 mins. This was allowed to stir at RT for 24 hr and completion of the reaction was confirmed by TLC. Diethyl ether was added to the reaction mixture which was poured into a separating funnel and washed with 25% $NaHSO_4$ (4 x 100 mL), followed by two 2M HCl washes and a brine wash, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by vacuum distillation, which afforded **165** as a pale yellow oil (333.4 g, 94% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.19 (d, J= 2.0 Hz, 1H, OC**H**=CH), 6.61 (d, J= 2.0 Hz, 1H, OCH=C**H**), 4.25 (q, J= 7.1 Hz, 2H, C**H$_2$**CH$_3$), 2.54 (s, 3H, CC**H$_3$**), 1.31 (t, J= 7.1 Hz, 3H, CH_2C**H$_3$**); **^{13}C NMR** (91 MHz, CDCl3) δ 164.2 (q), 159.2 (q), 140.3 (CH), 113.6 (q), 110.8 (CH), 60.1 (CH_2), 14.4 (CH_3), 13.7 (CH_3).

The spectroscopic data were in agreement with those previously published.[51,52]

(2-Methylfuran-3-yl)methanol **166**



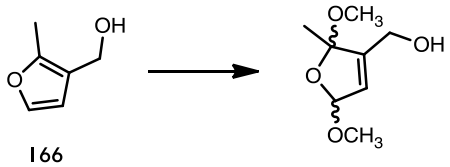
165 **166**

A mixture of lithium aluminium hydride (10.6 g, 0.28 mol, 1.2 equiv) and anhydrous Et_2O (300 mL) was stirred for 20 mins and cooled on ice. A solution of ethyl ester **165** (36 g, 0.23 mol, 1 equiv) in anhydrous Et_2O (230 mL) was added dropwise over a period of 1 hr under an atmosphere of inert N_2 gas. The temperature of the reaction did not exceed 28 °C during the addition of the ester. After all of the ester had been added, the reaction was left stirring at 0 °C for a further 1.5 hr at which time all of the starting material had completely disappeared by TLC. The reaction was then quenched with water (3.2 mL, 0.18 mol, 3 equiv), which was added dropwise over 20 mins during which time the temperature did not exceed 23 °C. The reaction mixture was then poured into diethyl ether (200 mL), dried over $MgSO_4$ and filtered. The unfiltered residue was extracted an additional four times with diethyl ether and all extracts were combined and evaporated under reduced pressure to yield alcohol **166** as a pale yellow oil (23.4 g, 91% yield). No further purification was required.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.9 Hz, 1H, OC**H**=CH), 6.35 (d, *J* = 1.9 Hz, 1H, OCH=C**H**), 4.45 (s, 2H, C**H$_2$**OH), 2.27 (s, 3H, C**H$_3$**); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 149.4 (q), 140.6 (CH), 118.9 (q), 111.0 (CH), 56.7 (CH_2), 11.6 (CH_3).

The spectroscopic data were in agreement with those previously published.[51,52]

(2,5-Dimethoxy-2-methyl-2,5-dihydrofuran-3-yl)methanol **167**



166 167

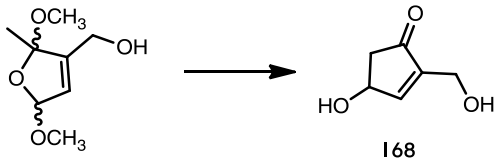
A solution of (2-methylfuran-3-yl)methanol **166** (87.5 g, 0.78 mol, 1 equiv) in MeOH:Et_2O (4:1, 600 mL) was cooled to –78 °C and stirred. A mixture of bromine in MeOH:Et_2O was made by slowly adding bromine (137.2 g, 0.86 mol, 1.1 equiv) to a solution of MeOH:Et_2O (4:1, 450 mL) that was cooled on ice. The solution of bromine was added dropwise to the reaction mixture during 1.5 hr. The reaction was left stirring for a further 1.5 hr, after which time the starting material had completely disappeared as confirmed by TLC. Triethylamine (272 mL, 1.95 mol, 2.5 equiv) was slowly added to the mixture, which was then allowed to warm to room temperature and left to stand for 1 hr. Et_2O (400 mL) was added to the reaction mixture which was filtered to remove salts and the filtrate was evaporated under reduced pressure to remove solvent. Salts were repeatedly precipitated from the crude product by adding diethyl ether (2 x 200 mL). The filtrate was then poured into a separating funnel containing diethyl ether (400 mL) and washed with brine (2 × 100 mL). The aqueous phases were re-extracted with DCM (2 x 200 mL) and the organic phases were combined, dried over $MgSO_4$ and evaporated under reduced pressure to yield a dark orange oil. Flash column chromatography (SiO_2, hexane/EtOAc 1:9) afforded a ~2:1 inseparable diastereomeric mixture of dihydrofuran **167** as a colourless clear oil (120.2 g, 89% yield).

Major diastereoisomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.92 – 5.89 (m, 1H, OC**H**CH=C), 5.46 – 5.43 (m, 1H, HCC**H**=C), 4.31 – 4.18 (m, 2H, CC**H_2**OH), 3.49 (s, 3H, CHOC**H_3**), 3.19 (s, 3H, COC**H_3**), 1.50 (s, 3H, CC**H_3**); **Minor diastereoisomer:** δ 5.95 – 5.92 (m, 1H, OC**H**CH=C), 5.73 – 5.71 (m, 1H, HCC**H**=C), 4.31 – 4.18 (m,

2H, CC**H**$_2$OH), 3.42 (s, 3H, OC**H**$_3$), 3.11 (s, 3H, OC**H**$_3$), 1.56 (s, 3H, CC**H**$_3$); **Major diastereoisomer:** **^{13}C NMR** (91 MHz, $CDCl_3$) δ 146.9 (q), 124.3 (CH), 111.2 (q), 106.1 (CH), 58.2 (CH_2), 56.3 (CH_3), 50.4 (CH_3), 25.4 (CH_3); **Minor diastereoisomer:** δ 147.4 (q), 124.6 (CH), 112.3 (q), 107.2 (CH), 58.2 (CH_2), 55.2 (CH_3), 49.8 (CH_3), 25.9 (CH_3).

The spectroscopic data were in agreement with those previously published.[51,52]

4-Hydroxy-2-(hydroxymethyl)cyclopent-2-enone **168**



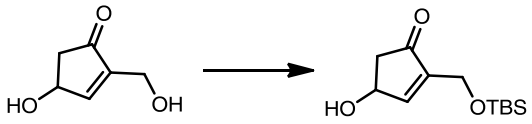
167 **168**

A solution of dihydrofuran **167** (17.3 g, 0.1 mol, 1 equiv) in 1,4-dioxane (110 mL) and 0.2 M potassium phosphate buffer (pH 6.3, 250 mL) was stirred and hydroquinone (0.17 g, 1.6 mmol, 0.016 equiv) was then added. This mixture was heated under reflux for 3.5 hr, after which time all of the starting material had disappeared by TLC. The solvent was evaporated by azeotropic distillation using ethanol, which left a residue that was extracted 8 times with boiling ethylacetate. The extracts were combined and evaporated under reduced pressure, which left a dark orange oil. Flash column chromatography (SiO_2, EtOAc/MeOH 19:1) gave racemate **168** as a pale off-white solid (9.09 g, 71% yield).

^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.32 – 7.28 (m, 1H, C**H**=C), 4.90 – 4.81 (m, 1H, C**H**OH), 4.39 (d, J = 5.9 Hz, 1H, CHO**H**), 4.18 – 4.13 (m, 2H, CC**H**$_2$OH), 4.00 (t, J = 5.5 Hz, 1H, CH_2O**H**), 2.66 (dd, $J_{AB, AX}$ = 18.3, 6.0 Hz, 1H, C**H**$_2$CO), 2.12 (dd, $J_{BA, BX}$ = 18.3, 2.0 Hz, 1H, C**H**$_2$CO); **^{13}C NMR** (91 MHz, CD_3COCD_3) δ 207.2 (q), 158.5 (CH), 148.4 (q), 69.4 (CH), 57.6 (CH_2), 46.7 (CH_2).

The spectroscopic data were in agreement with those previously published.[51,52]

2-((*tert*-butyldimethylsilyloxy)methyl)-4-hydroxycyclopent-2-enone **172**



168 **172**

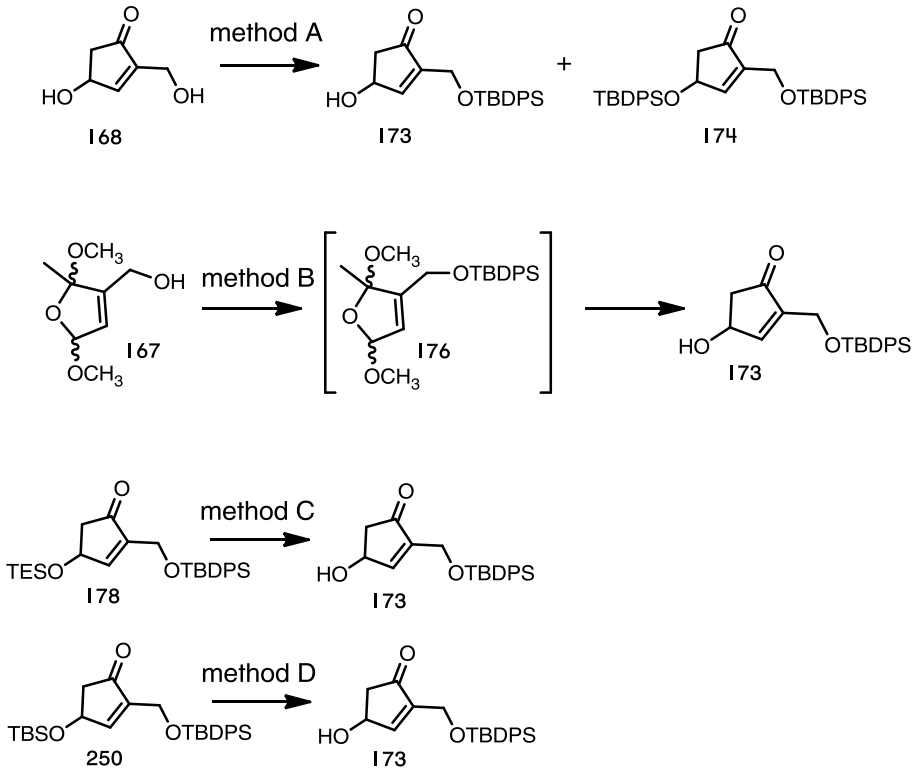
Method A: A solution of cyclopentenone-diol **168** (120 mg, 0.94 mmol, 1 equiv), imidazole (134 mg, 1.96 mmol, 2.1 equiv) and DMAP (11.4 mg, 0.093 mmol, 0.1 equiv) was dissolved in dry DMF (4 mL) and was stirred for 10 mins under an atmosphere of N_2. This mixture was then cooled to 0 °C at which time a solution of TBSCl (155 mg, 1.03 mmol, 1.1 equiv) in dry DMF (2 mL) was cannulated dropwise into the reaction mixture. The reaction was left for 24 hr at RT, after which time most of the starting material had disappeared as confirmed by TLC. The reaction was quenched with water (1 mL) and poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (1 x 20 mL) and followed by a brine wash (2 x 20 mL). The aqueous phases were saturated with NaCl and re-extracted twice with EtOAc. This left an orange oil which was poured into a separating funnel containing Et_2O (150 mL). The organic layer was washed with distilled water (4 x 10 mL) to remove any remaining DMF. The aqueous layers were saturated with NaCl and re-extracted twice with Et_2O. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 6:4) furnished enone **172** as a white crystalline solid (91 mg, 41% yield).

Method B: A solution of cyclopentenone-diol **168** (200 mg, 1.56 mmol, 1 equiv) was dissolved in dry DMF (5 mL) and was stirred for 10 mins under an atmosphere of inert N_2. This was then cooled to -45 °C, at which time a solution of TBSOTf (430 mg, 4.64 mmol, 1.05 equiv) and 2,6-lutidine (0.35 g, 3.28 mmol, 2.1 equiv) in dry DMF (1 mL) was cannulated dropwise into the reaction mixture. The reaction was left for 45 mins, after which time all of the starting material had disappeared as

confirmed by TLC. The reaction mixture was raised to RT, quenched with water (5 mL) and poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (1 x 20 mL) followed by a brine wash (2 x 20 mL). The aqueous phases were saturated with NaCl and re-extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. This left a colourless oil which was poured into a separating funnel containing Et_2O (150 mL). The organic layer was washed with water (4 x 10 mL) to remove any remaining DMF. The aqueous layers were saturated with NaCl and re-extracted twice with Et_2O. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 6:4) delivered **172** as a white crystalline solid (170 mg, 45% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H, C**H**=C), 5.01 – 4.87 (m, 1H, C**H**OH), 4.33 (t, J = 2.1 Hz, 2H, C**H$_2$**OSi), 2.81 (dd, $J_{AB,\ AX}$ = 18.6, 6.0 Hz, 1H, C**H$_2$**CO), 2.32 (dd, $J_{BA,\ BX}$ = 18.6, 2.0 Hz, 1H, C**H$_2$**CO), 0.88 (s, 9H, SiC(C**H$_3$**)$_3$), 0.09-0.00 (m, 6H, 2 x SiC**H$_3$**); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 205.1 (q), 156.5 (CH), 147.7 (q), 68.4 (CH), 57.7 (CH_2), 45.5 (CH_2), 25.8 (CH_3), 18.2 (q). -5.6 (CH_3), -5.5 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3419, 2929, 2251, 1705, 1471; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{23}O_3Si$ $[M+H]^+$ 243.1411, found 243.1408; **MP** 32-34 °C.

2-((*tert-B*utyldiphenylsilyloxy)methyl)-4-hydroxycyclopent-2-enone **173**, 4-(*tert*-Butyldiphenylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)cyclopent-2-enone **174** and *tert*-Butyl((2,5-dimethoxy-2-methyl-2,5-dihydrofuran-3-yl)methoxy)diphenylsilane **176**



Method A: A solution of cyclopentenone-diol **168** (300 mg, 2.34 mmol, 1 equiv), imidazole (351 mg, 5.15 mmol, 2.2 equiv) and DMAP (57 mg, 0.47 mmol, 0.2 equiv) in dry DMF (1 mL) was stirred for 10 mins under an atmosphere of inert nitrogen gas. This mixture was then cooled to 0 °C at which time a solution of TBDPSCl (680 mg, 2.46 mmol, 1.1 equiv) in dry DMF (1 mL) was cannulated dropwise into the reaction mixture. The reaction was left for 6 hr at RT, after which time most of the starting material had disappeared as confirmed by TLC. The reaction was quenched with water (1 mL) and poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (1 x 20 mL) and followed by a brine wash (2 x 20 mL). The aqueous phases were saturated with NaCl and re-

extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. This left an orange oil which was poured into a separating funnel containing Et_2O (150 mL). The organic layer was washed with water (4 x 10 mL) to remove any remaining DMF. The aqueous layers were saturated with NaCl and re-extracted twice with Et_2O. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 6:4) afforded enone **173** as a white crystalline solid (0.34 g, 40% yield) and byproduct **174** as a white crystalline solid (0.32 g, 23% yield).

Method B: A solution of alcohol **167** (0.6 g, 3.44 mmol, 1 equiv), imidazole (0.49 g, 7.23 mmol, 2.1 equiv) and DMAP (0.08 g, 0.69 mmol, 0.2 equiv) in dry DMF (8 mL) was stirred for 10 mins under an atmosphere of inert nitrogen gas. This mixture was then cooled to 0 °C at which time a solution of TBDPSCl (0.99 g, 3.62 mmol, 1.1 equiv) in dry DMF (1 mL) was cannulated dropwise into the reaction mixture. The reaction was allowed to warm to room temperature for 4 hr, after which time all of the starting material had disappeared as confirmed by TLC. The reaction was quenched with water (5 mL) and poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (1 x 20 mL) and followed by a brine wash (2 x 20 mL). The aqueous phases were saturated with NaCl and re-extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. A sample of the crude dihydrofuran **176** was was purified by flash column chromatography (SiO_2, hexane/EtOAc 1:9) and used for characterisation. The remaining crude **176** was sufficiently pure to be used in the following step. A solution of the crude **176** (0.47 g, 1.14 mmol, 1 equiv) in DMF (10 mL) and 0.2 M potassium phosphate buffer (pH 6.3, 5 mL) was stirred and hydroquinone (0.002 g, 0.018 mmol, 0.016 equiv) was then added. This mixture was heated under reflux for 24 hr, after which time the water was evaporated by azeotropic distillation using ethanol, which left a residue that was

extracted 8 times with boiling ethylacetate. The extracts were combined and evaporated under reduced pressure. This left an orange oil which was purified by flash column chromatography (SiO_2, hexane/EtOAc 6:4) to furnish alcohol **173** as a white crystalline solid (0.13 g, 30% yield over two steps).

Method C: A solution of *bis*-protected **178** (75 mg, 0.16 mmols, 1 equiv) was dissolved in MeCN:H_2O, 9:1 (0.56 mL) under nitrogen before addition of DDQ (4 mg, 0.016 mmols, 0.1 equiv) in MeCN:H_2O (9:1, 0.56 mL). The resulting mixture was left to stir for 1 hr at room temperature, after which time all of the starting material had disappeared as confirmed by TLC. Subsequently, the reaction mixture was evaporated under reduced pressure to leave a residue which was purified by flash column chromatography (SiO_2, hexane/EtOAc 6:4) and gave **173** as a white crystalline solid (45.5 mg, 80% yield).

Method D: A solution of cyclopentenone **244** (4.4 g, 9.2 mmol, 1 equiv) in THF:H_2O (60 mL, 9:1) was treated with DDQ (311 mg, 1.37 mmol, 0.15 equiv) and stirred at 40 °C for 22 hr before adding an excess of saturated NH_4Cl solution. EtOAc extractions followed by drying over $MgSO_4$, filtering and solvent removal afforded a crude mixture which was purified by flash column chromatography (SiO_2, hexane/EtOAc 6:4) to afford secondary alcohol **173** as a white crystalline solid (2.84 g, 85% yield).

Dihydrofuran 176, major diastereoisomer: **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.75 – 7.62 (m, 4H, Ar**H**), 7.51 – 7.32 (m, 6H, Ar**H**), 6.08 – 6.04 (m, 1H, OC**H**CH=C), 5.49 – 5.45 (m, 1H, HCC**H**=C), 4.33 – 4.15 (m, 2H, CC**H$_2$**OH), 3.52 (s, 3H, CHOC**H$_3$**), 3.07 (s, 3H, COC**H$_3$**), 1.39 (s, 3H, CC**H$_3$**), 1.10 (s, 9H, SiC(C**H$_3$**)$_3$); The ^{1}H NMR signals of the minor diastereoisomer were too weak to be confidently assigned; **Major diastereoisomer:** **^{13}C NMR** (91 MHz, $CDCl_3$) δ 146.5 (q), 135.6 (CH), 135.6 (CH), 133.2 (q), 133.0 (q), 130.0 (CH), 130.0 (CH), 127.9 (CH), 124.2 (CH), 110.8 (q), 105.9 (CH), 59.6 (CH_2), 56.1 (CH_3), 50.0 (CH_3), 26.9 (CH_3), 25.5 (CH_3), 19.4 (q);

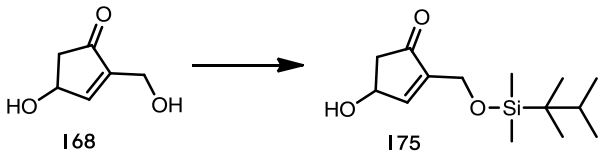
The ^{13}C NMR signals of the minor diastereoisomer were too weak to be confidently assigned; **IR** (thin film, NaCl plate, cm^{-1}); 2932, 1589, 1472, 1428, 1367; **HRMS** (ESI) *m/z* calcd for $C_{24}H_{36}NO_4Si$ $[M+NH_4]^+$ 430.2408, found 430.2405; **MP** 54-56 °C.

Mono-protected 173: ^1H **NMR** (360 MHz, $CDCl_3$) δ 7.72 – 7.60 (m, 4H, Ar**H**), 7.51 – 7.47 (m, 1H, C**H**=C), 7.47 – 7.34 (m, 6H, Ar**H**), 5.00 – 4.89 (m, 1H, C**H**OH), 4.49 – 4.39 (m, 2H, C$\mathbf{H_2}$OSi), 2.80 (dd, $J_{AB,\ AX}$ = 18.6, 6.0 Hz, 1H, C$\mathbf{H_2}$CO), 2.45 (s, 1H, CHO**H**), 2.31 (dd, $J_{BA,\ BX}$ = 18.6, 1.9 Hz, 1H, C$\mathbf{H_2}$CO), 1.09 (s, 9H, SiC(C$\mathbf{H_3}$)$_3$); ^{13}**C NMR** (63 MHz, $CDCl_3$) δ 204.8 (q), 156.2 (CH), 147.7 (q), 135.6 (CH), 135.6 (CH), 133.1 (q), 130.0 (CH), 127.9 (CH), 68.7 (CH), 58.8 (CH_2), 45.6 (CH_2), 26.9 (CH_3), 19.4 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3426, 2931, 2859, 2250, 1702, 1112; **HRMS** (ESI) *m/z* calcd for $C_{22}H_{30}NO_3Si$ $[M+NH_4]^+$ 384.1989, found 384.1989; **MP** 38-40 °C.

***Bis*-protected 174:** ^1H **NMR** (360 MHz, $CDCl_3$) δ 7.81 – 7.58 (m, 8H, Ar**H**), 7.53 – 7.28 (m, 13H, 12 × Ar**H**, C**H**=C), 4.95 – 4.88 (m, 1H, C**H**OSi), 4.49 – 4.32 (m, 2H, C$\mathbf{H_2}$OSi), 2.63 (dd, $J_{AB,\ AX}$ = 18.4, 5.8 Hz, 1H, C$\mathbf{H_2}$CO), 2.46 (dd, $J_{BA,\ BX}$ = 18.4, 2.1 Hz, 1H, C$\mathbf{H_2}$CO), 1.13 (s, 9H, SiC(**CH$_3$**)$_3$), 1.09 (s, 9H, SiC(**CH$_3$**)$_3$); ^{13}**C NMR** (91 MHz, $CDCl_3$) δ ppm 204.6 (q), 156.9 (CH), 146.9 (q), 135.6 (CH), 135.5 (CH), 133.6 (q), 133.3 (q), 133.1 (q), 133.0 (q), 130.2 (CH), 130.0 (CH), 129.9 (CH), 128.0 (CH), 127.9 (CH), 70.0 (CH), 58.8 (CH_2), 46.1 (CH_2), 27.0 (CH_3), 19.4 (q), 19.1 (q); **IR** (thin film, NaCl plate, cm^{-1}) 2931, 2858, 1708, 1472, 1428, 1112; **HRMS** (ESI) *m/z* calcd for $C_{38}H_{45}O_3Si_2$ $[M+H]^+$ 605.2902, found 605.2901; **MP** 88-90 °C

2-(((2,3-Dimethylbutan-2-yl)dimethylsilyloxy)methyl)-4-hydroxycyclopent-2-enone

175

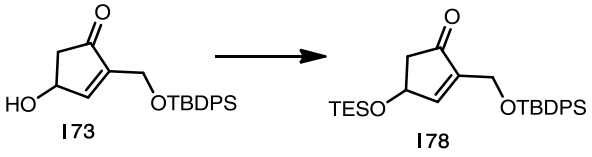


A solution of cyclopentenone-diol **168** (0.15 g, 1.17 mmol, 1 equiv), imidazole (0.17 g, 2.46 mmol, 2.1 equiv) and DMAP (0.03 g, 0.23 mmol, 0.2 equiv) in dry DMF (1 mL) was stirred for 10 mins under an atmosphere of inert nitrogen gas. This mixture was then cooled to 0 °C, at which time a solution of TDSCl (0.22 g, 1.23 mmol, 1.05 equiv) in dry DMF (2 mL) was cannulated dropwise into the reaction mixture. The reaction was left for 24 hr, after which time most of the starting material had disappeared as confirmed by TLC. The reaction was quenched with water (1 mL) and poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (1 x 20 mL) and followed by a brine wash (2 x 20 mL). The aqueous phases were saturated with NaCl and re-extracted twice with EtOAc. This left an orange oil which was poured into a separating funnel containing Et_2O (150 mL).The organic layer was washed with water (4 x 10 mL) to remove any remaining DMF. The aqueous layers were saturated with NaCl and re-extracted twice with Et_2O. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure. This left an orange oil which was purified by flash column chromatography (SiO_2, hexane/EtOAc 6:4) to afford **175** as a deep orange clear oil (0.13 g, 41% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 1H, C**H**=C), 5.03 – 4.92 (m, 1H, C**H**OH), 4.34 (s, 2H, C**H$_2$**OSi), 2.83 (dd, $J_{AB,\,AX}$ = 18.6, 5.9 Hz, 1H, C**H$_2$**CO), 2.53 (s. br, 1H, C**H**OH), 2.34 (dd, $J_{BA,\,BX}$ = 18.6, 1.7 Hz, 1H, C**H$_2$**CO), 1.71 – 1.56 (m, 1H, C**H**C(CH$_3$)$_2$), 0.96 – 0.80 (m, 12H, C(C**H$_3$**)$_2$C(C**H$_3$**)$_2$), 0.16 – 0.04 (m, 6H, 2 × SiC**H$_3$**); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 205.1 (q), 156.3 (CH), 148.2 (q), 68.7 (CH), 57.8 (CH_2),

45.7 (CH_2), 34.3 (CH) 25.3 (q), 20.4 (CH_3), 18.6 (CH_3), -3.4 (CH_3), -3.5 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3421, 2959, 1700, 1466, 1397, 1254; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{27}O_3Si$ $[M+H]^+$ 271.1724, found 271.1729.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-4-(triethylsilanyloxy)cyclopent-2-enone **178**

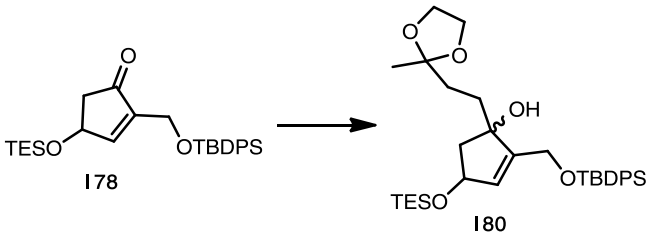


Enone **173** (5.6 g, 15.3 mmol, 1 equiv), triethylamine (5.83 mL, 41.7 mmol, 2.73 equiv) and DMAP (187 mg, 1.53 mmol, 0.1 equiv) were dissolved in dry DCM (25 mL) and cooled to 0°C before addition of TESCl (2.99 g, 19.9 mmol, 1.3 equiv) under an inert atmosphere of N_2. The resulting mixture was then heated under reflux for 24hr, after which time the starting material had disappeared as confirmed by TLC. The reaction was quenched with water (5 mL) and was poured into a separating funnel containing EtOAc (75 mL). The organic layer was washed with saturated NH_4Cl (2 x 20 mL) and followed by a brine wash (2 x 20 mL). The aqueous phases were re-extracted with EtOAc and the organic phases were combined, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. This left an orange oil which was purified by flash column chromatography (SiO_2, hexane/EtOAc 19:1) to give enone **178** as a pale yellow oil (7.05 g, 96% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H, Ar**H**), 7.48 – 7.35 (m, 7H, 6 × ArC**H**, C**H**=C), 4.97 – 4.90 (m, 1H, C**H**OSi), 4.44 (t, J = 2.1 Hz, 2H, C**H$_2$**OSi), 2.78 (dd, $J_{AB, AX}$ = 18.3, 5.9 Hz, 1H, C**H$_2$**CO), 2.35 (dd, $J_{BA, BX}$ = 18.3, 2.1 Hz, 1H, C**H$_2$**CO), 1.11 (s, 9H, SiC(C**H$_3$**)$_3$), 1.02 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H$_3$**)$_3$), 0.69 (q, J = 7.6 Hz, 6H, Si(C**H$_2$**CH$_3$)$_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 204.7 (q), 157.0 (CH), 147.0 (q), 135.6 (CH), 135.6 (CH), 133.2 (q), 133.1 (q), 130.0 (CH), 130.0 (CH), 127.9 (CH),

68.9 (CH), 58.9 (CH_2), 46.3 (CH_2), 26.9 (CH_3), 19.4 (q) , 6.8 (CH_3), 4.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2956, 1714, 1589, 1471, 1427, 1112; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{44}NO_3Si_2$ $[M+NH_4]^+$ 498.2854, found 498.2852.

2-(*tert*-Butyldiphenylsilanyloxymethyl)-1-[2-(2-methyl[1,3]dioxolan-2-yl)ethyl]-4-(triethylsilanyloxy)cyclopent-2-enol **180**

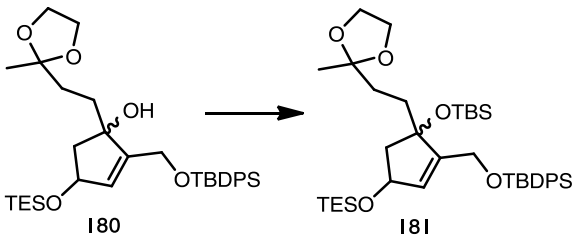


2-(2-Iodoethyl)-2-methyl[1,3]dioxolane **147** (0.81 g, 3.33 mmol, 1.6 equiv) was dissolved in dry Et_2O (18 mL), cooled to –78 °C under an atmosphere of N_2 before slow addition of ^{t}BuLi (4.16 mL, 1.7 M in pentane, 7.1 mmol, 3.4 equiv). The resulting mixture was stirred at –78 °C under N_2 for 1 hr before warming to room temperature and stirring for another 1 hr. At which time, the mixture was cannulated into a solution of cyclopentenone **178** (1 g, 2.08 mmol, 1 equiv) in dry Et_2O (18 mL) at –78°C during 20 mins. The resulting reaction mixture was stirred at –78 °C for 3 hr before warming to room temperature and left for 30 mins. After this time, the reaction was quenched with water (10 mL) and poured into a separating funnel containing saturated NH_4Cl solution (40 mL) and EtOAc (250 mL). The organic layer was washed with brine (2 x 40 mL) and the aqueous layer re-extracted twice with EtOAc before combining the organic layers which were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished a single diastereomer of tertiary alcohol **180** as an oil (1.03 g, 83% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 4H, Ar**H**), 7.48 – 7.33 (m, 6H, Ar**H**), 5.83 – 5.79 (m, 1H, C**H**=C), 4.66 – 4.54 (m, 1H, C**H**OSi), 4.45 – 4.24 (m, 2H,

C**H**$_2$OSi), 3.99 – 3.72 (m, 4H, OC**H**$_2$C**H**$_2$O), 2.56 (s, 1H, CH$_2$CO**H**), 2.43 (dd, $J_{AB, AX}$ = 13.7, 6.8 Hz, 1H, C**H**$_2$COH), 1.86 – 1.41 (m, 5H, C**H**$_2$COH, CC**H**$_2$C**H**$_2$), 1.26 (s, 3H, C**H**$_3$CCH$_2$), 1.07 (s, J = 3.6 Hz, 9H, SiC(C**H**$_3$)$_3$), 0.98 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.62 (q, J = 7.9 Hz, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 149.2 (q), 135.7 (CH), 135.7 (CH), 133.2 (q), 130.6 (CH), 129.9 (CH), 129.9 (CH), 127.9 (CH), 109.9 (q), 83.4 (q), 73.2 (CH), 64.7 (CH_2), 60.6 (CH_2), 49.4 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 26.9 (CH_3), 23.9 (CH_3), 19.3 (q), 6.9 (CH_3), 4.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3455, 2929, 2359, 1777, 1589, 1463; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{56}NO_5Si_2$ $[M+NH_4]^+$ 614.3692, found 614.3694.

tert-Butyl((5-(*tert*-butyldimethylsilyloxy)-5-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-3-(triethylsilyloxy)cyclopent-1-enyl)methoxy)diphenylsilane **181**

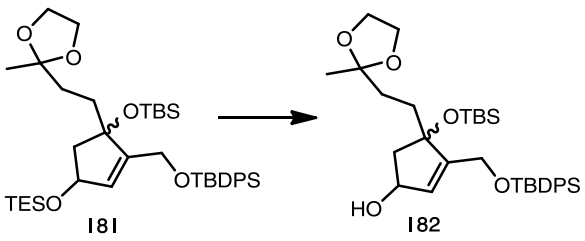


Tertiary alcohol **180** (5.80 g, 9.7 mmol, 1 equiv) was dissolved in dry DMF (30 mL) and cooled to 0 °C under an atmosphere of N_2. The resulting mixture was stirred for 5 mins before dropwise addition of a solution containing TBSOTf (12.95 g, 48.5 mmol, 5 equiv) and 2,6-lutidine (11 g. 102.8 mmol, 10.5 equiv) in dry DMF (5 mL). The reaction mixture was stirred for 20 mins before warming to RT and left for a further 2 hr until the reaction was complete as confirmed by TLC. This was then poured into a separating funnel containing saturated NH_4Cl solution (20 mL) and extracted with Et_2O (100 mL). The organic layer was washed with distilled water (2 x 20 mL) and the aqueous fractions were combined and again extracted twice with Et_2O (2 x 100mL). The organic fractions were combined, dried over $MgSO_4$, filtered

and concentrated *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 19:1) supplied TBS ether **181** as a white crystalline solid (6.85 g, 99% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 4H, Ar**H**), 7.47 – 7.33 (m, 6H, Ar**H**), 5.88 – 5.84 (m, 1H, C**H**=C), 4.70 – 4.59 (m, 1H, C**H**OSi)), 4.45 – 4.16 (m, 2H, C**H$_2$**OSi), 3.96 – 3.76 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.48 (dd, *J* = 13.3, 7.0 Hz, 1H, C**H$_2$**CO), 1.96 (dd, *J* = 13.3, 5.1 Hz, 1H, C**H$_2$**CO), 1.73 – 1.33 (m, 4H, CH_3CC**H$_2$C H$_2$**), 1.24 (s, 3H, C**H$_3$**CCH_2), 1.08 (s, 9H, CH_2OSiC(C**H$_3$)$_3$**), 1.00 (t, *J* = 7.9 Hz, 9H, $Si(CH_2C$**H$_3$)$_3$**), 0.75 (s, 9H, $COSiC$(C**H$_3$)$_3$**), 0.64 (q, *J* = 7.6 Hz, 6H, Si(C**H$_2$**CH_3)$_3$**), 0.04 (s, 3H, SiC**H$_3$**), 0.01 (s, 3H, SiC**H$_3$**); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 150.4 (q), 135.7 (CH), 135.6 (CH), 133.9 (q), 133.6 (q), 129.8 (CH), 129.7 (CH), 128.5 (CH), 127.8 (CH), 127.8 (CH), 110.1 (q), 84.9 (q), 73.6 (CH), 64.7 (CH_2), 64.7 (CH_2), 60.2 (CH_2), 50.1 (CH_2), 35.7 (CH_2), 34.0 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 23.9 (CH_3), 19.4 (q), 18.3 (q), 7.0 (CH_3), 5.1 (CH_2), -2.1 (CH_3), -2.9 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2956, 2251, 1462; **HRMS** (ESI) *m/z* calcd for $C_{40}H_{70}NO_5Si_3$ $[M+NH_4]^+$ 728.4556, found 728.4563; **MP** 74-76 °C.

4-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol **182**

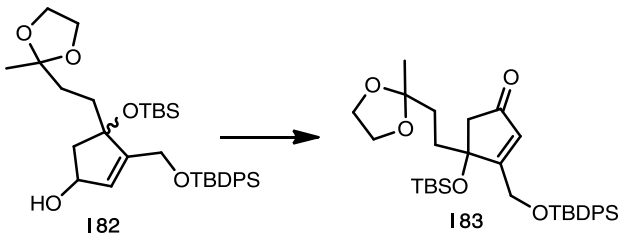


Cyclopentene **181** (5.7 g, 8.04 mmol, 1 equiv) was dissolved in a solution of THF:H_2O (9:1, 35 mL) and stirred for 10 mins at RT. TCNQ (164 mg, 0.80 mmol, 0.1 equiv) was subsequently added to the resulting mixture and stirred for 24 hr until the reaction was complete as confirmed by TLC. The reaction mixture was then poured into a separating funnel containing saturated NH_4Cl solution (1 x 20 mL) and

extracted with EtOAc (1 x 150 mL). The organic layer was washed with brine (2 x 20 mL) and the aqueous layers were combined and re-extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$ and removed under reduced pressure. Residual TCNQ was removed by triturating three times with Et_2O and filtering off the solid residue. Evaporation of the solvent under reduced pressure gave a yellow oil which was purified by flash column chromatography (SiO_2, hexane/EtOAc 7:3) to afford secondary alcohol **182** as a clear crystalline solid (4.2 g, 88% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.76 – 7.64 (m, 4H, Ar**H**), 7.49 – 7.33 (m, 6H, ArC**H**), 5.98 – 5.92 (m, 1H, C**H**=C), 4.64 (s, 1H, C**H**OH), 4.47 – 4.18 (m, 2H, C**H$_2$**OSi), 3.96 – 3.75 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.58 (dd, $J_{AB, AX}$ = 13.5, 7.0 Hz, 1H, C**H$_2$**COSi), 1.88 (dd, $J_{BA, BX}$ = 13.5, 5.1 Hz, 1H, C**H$_2$**COSi), 1.80 – 1.34 (m, 5H, CC**H$_2$**C**H$_2$**, CH_2CO**H**), 1.23 (s, 3H, C**H$_3$**CCH_2), 1.09 (s, 9H, $CH_2OSiC(CH_3)_3$), 0.75 (s, 9H, $COSiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 152.1 (q), 135.6 (CH), 135.6 (CH), 133.6 (q), 133.6 (q), 129.8 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 109.9 (q), 85.2 (q), 73.8 (CH), 64.7 (CH_2), 64.7 (CH_2), 60.1 (CH_2), 50.0 (CH_2), 35.2 (CH_2), 34.0 (CH_2), 27.0 (CH_3), 25.8 (CH_3), 23.9 (CH_3), 19.4 (q), 18.2 (q), -2.1 (CH_3), -2.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3452, 3072, 2856, 2247, 1959, 1589, 1471; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{56}NO_5Si_2$ $[M+NH_4]^+$ 614.3692, found 614.3688; **MP** 52-54 °C.

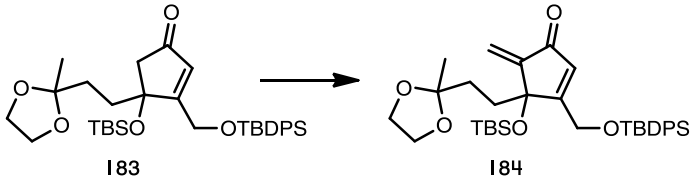
4-(*tert-B*utyldimethylsilyloxy)-3-((tert-butyldiphenylsilyloxy)methyl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone **183**



Alcohol **182** (1.0 g, 1.67 mmol, 1 equiv) and $NaHCO_3$ (0.70 g, 8.38 mmol, 5 equiv) was dissolved in dry DCM (10 mL) and stirred for 10 mins at RT before addition of DMP (1.07 g, 2.51 mmol, 1.5 equiv). The resulting mixture was stirred for 2.5 hr until the reaction was complete as confirmed by TLC. The reaction mixture was then poured into a separating funnel containing brine (1 × 20 mL) and DCM (100 mL). The organic layer was separated, washed again with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 3:1) furnished enone **183** as a white solid (0.92 g, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 4H, Ar**H**), 7.49 – 7.34 (m, 6H, Ar**CH**), 6.39 (s, 1H, C=C**H**), 4.65 (d, *J* = 18.7 Hz, 1H, C**H$_2$**OSi), 4.45 (d, *J* = 18.7 Hz, 1H, C**H$_2$**OSi), 3.92 – 3.73 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.57 (s, 2H, C**H$_2$**CO), 1.84 – 1.30 (m, 4H, CC**H$_2$**C**H$_2$**), 1.21 (s, 3H, C**H$_3$**CCH$_2$), 1.08 (s, 9H, CH$_2$OSiC(C**H$_3$**)$_3$), 0.73 (s, 9H, COSiC(C**H$_3$**)$_3$), 0.02 (s, 3H, SiC**H$_3$**), -0.05 (s, 3H, SiC**H$_3$**); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.2 (q), 182.6 (q), 135.6 (CH), 135.5 (CH), 133.0 (q), 132.8 (q), 130.1 (CH), 128.3 (CH), 128.0 (CH), 109.5 (q), 80.7 (q), 64.8 (CH_2), 60.4 (CH_2), 50.0 (CH_2), 34.9 (CH_2), 34.1 (CH_2), 26.9 (CH_3), 25.7 (CH_3), 24.0 (CH_3), 19.4 (q), 18.1 (q), -2.4 (CH_3), -3.0 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2251, 1716, 1631, 1255; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{50}O_5Si_2Na$ $[Na]^+$ 617.3089, found 617.3085; **MP** 46-48 °C.

4-(*tert-B*utyldimethylsilyloxy)-3-((tert-butyldiphenylsilyloxy)methyl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-methylenecyclopent-2-enone **184**



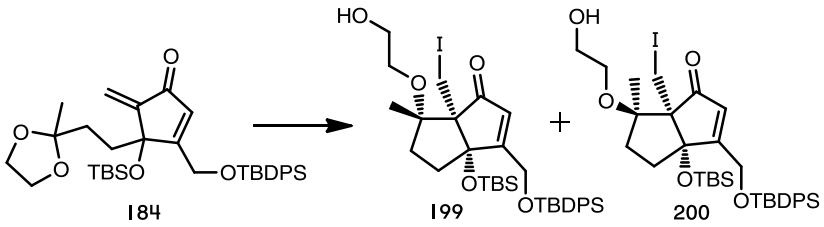
Cyclopentenone **183** (500 mg, 0.84 mmol, 1 equiv) was dissolved in dry THF (15 mL) under N_2, cooled to –78 °C and stirred for 10 mins before slow addition of LDA (1.4 mL, 1.8M in THF/heptane/ethylbenzene, 2.52 mmol, 3 equiv) and left to stir for a further hr. The resulting solution was then cannulated dropwise over 10 mins to a mixture of Eschenmoser's salt (466 mg, 2.52 mmol, 3 equiv) in dry THF (7.5 mL), which was pre-cooled to –78 °C. The reaction was left at –78 °C for 2 hr before allowing to warm to RT and stirred for a further 30 mins. The reaction mixture was then poured into a separating funnel containing Et_2O (75 mL) and saturated $NaHCO_3$ (25 mL). The aqueous phase was re-extracted with DCM (2 x 75 mL) and the organic fractions were combined and evaporated under reduced pressure. The crude orange residue was dissolved in a mixture of DCM (10 mL) and $NaHCO_3$ (5 mL). Under vigorous stirring, one portion of *m*CPBA (435 mg, 2.52 mmol, 3 equiv) was added and left to stir for 1 hr before separating the organic layer. The aqueous layer was extracted with DCM and the combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure leaving an orange crude oil. Flash column chromatography (SiO_2, Hexane/EtOAc 85:15) afforded **184** as a white solid (351 mg, 67 % yield over two steps).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.76 – 7.61 (m, 4H, Ar**H**), 7.51 – 7.34 (m, 6H, Ar**CH**), 6.67 (s, 1H, C=**CH**), 6.17 (s, 1H, **CH$_2$**=C), 5.50 (s, 1H, **CH$_2$**=C), 4.67 (dd, $J_{AB,\ AX}$ = 18.9, 1.6 Hz, 1H, **CH$_2$**OSi), 4.45 (dd, $J_{BA,\ BX}$ = 19.0, 1.8 Hz, 1H, **CH$_2$**OSi), 3.93 – 3.63 (m, 4H, O**CH$_2$CH$_2$**O), 1.93 (td, J = 13.1, 4.3 Hz, 1H, **CH$_2$**), 1.67 (td, J = 12.9, 4.2 Hz, 1H, **CH$_2$**), 1.29 (td, J = 13.0, 4.2 Hz, 1H, **CH$_2$**), 1.16 (s, 3H, **CH$_3$**CCH$_2$), 1.09 (s, 10H,

9 × $CH_2OSiC(CH_3)_3$, CH_2), 0.74 (s, 9H, $COSiC(CH_3)_3$), -0.08 (s, 3H, $Si(CH_3)$, -0.15 (s, 3H, $SiCH_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 193.6 (q), 177.8 (q), 148.3 (q), 135.6 (CH), 135.5 (CH), 132.8 (q), 130.2 (CH), 130.1 (CH), 130.1 (CH), 128.0 (CH), 117.3 (CH_2), 109.4 (q), 79.8 (q), 64.6 (CH_2), 60.2 (CH_2), 33.9 (CH_2), 33.3 (CH_2), 26.8 (CH_3), 25.8 (CH_3), 23.7 (CH_3), 19.4 (q), 18.3 (q), -2.5 (CH_3), -3.3 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3070, 2931, 1705, 1657, 1618, 1252; **Elemental Analysis** (%, w/w) calcd for $C_{35}H_{50}O_5Si_2$ C(69.3), H(8.30), found C(68.8), H(8.31); **HRMS** (ESI) *m/z* calcd for $C_{35}H_{54}NO_5Si_2$ $[M+NH_4]^+$ 624.3535, found 624.3524; **MP** 82-84 °C.

3a-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-6-(2-hydroxyethoxy)-6a-(iodomethyl)-6-methyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one

199 and **200**



184 199 200

TBAI (292 mg, 0.79 mmol, 1.2 equiv) was dissolved in dry DCM (5 mL) under N_2, cooled to 0 °C and left to stir for 10 mins. $TiCl_4$ (2.64 mL, 1 M in DCM, 2.64 mmol, 4 equiv) was added dropwise over a period of 10 mins to the cooled mixture and the resulting dark-red solution was left to stir for a further 5 mins before being warmed to RT. To the reaction mixture a solution of *exo*-methylene **184** (400 mg, 0.66 mmol, 1 equiv) in dry DCM (10 mL) at RT was cannulated dropwise over 15 mins. The reaction was left to stir for a further 1 hr at which time the reaction was quenched with saturated NH_4Cl aqueous solution (15 mL). This was poured into a separating funnel and the organic phase was washed with brine and the aqueous phases were combined and re-extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure to leave

a crude mixture which was further purified by flash column chromatography (SiO_2, hexane/EtOAc, 6:4) which afforded a separable diastereomeric mixture of **199:200** (5:1) (d.r. calculated from ^{1}H-NMR of crude). Major diastereomer **199** (304 mg, 63% yield) and minor diastereomer **200** (79 mg, 16% yield) were both obtained as a brown oil in a combined overall yield of 79% (383 mg).

Major diastereoisomer 199: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H, Ar**H**), 7.46 – 7.33 (m, 6H, Ar**H**), 6.41 – 6.39 (m, 1H, C=C**H**), 4.66 (dd, $J_{AB, AX}$ = 18.5, 1.8 Hz, 1H, C**H**$_2$OSi), 4.43 (dd, $J_{BA, BX}$ = 18.5, 1.6 Hz, 1H, C**H**$_2$OSi), 3.75 – 3.60 (m, 2H, OC**H**$_2$C**H**$_2$O), 3.53 – 3.44 (m, 2H, OCH$_2$C**H**$_2$O, C**H**$_2$I), 3.33 – 3.23 (m, 2H, OCH$_2$C**H**$_2$O, C**H**$_2$I), 1.96 (td, J = 12.8, 6.3 Hz, 1H, CH$_3$CCH$_2$C**H**$_2$), 1.88 (dd, J = 14.0, 6.2 Hz, 1H, CH$_3$CC**H**$_2$CH$_2$), 1.68 (dd, J = 12.4, 6.3 Hz, 1H, CH$_3$CCH$_2$C**H**$_2$), 1.35 (s, 3H, C**H**$_3$CCH$_2$), 1.10 (s, 9H, CH$_2$OSiC(C**H**$_3$)$_3$), 1.00 (td, J = 13.7, 6.4 Hz, 1H, CH$_3$CC**H**$_2$CH$_2$), 0.77 (s, 9H, COSiC(C**H**$_3$)$_3$), 0.07 (s, 3H, SiC**H**$_3$), -0.15 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 205.4 (q), 180.5 (q), 135.9 (CH), 133.4 (q), 132.9 (q), 130.4 (CH), 130.4 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 90.0 (q), 85.6 (q), 67.6 (q), 62.4 (CH_2), 62.3 (CH_2), 62.0 (CH_2), 35.6 (CH_2), 33.0 (CH_2), 27.2 (CH_3), 26.3 (CH_3), 19.7 (q), 18.9 (q), 17.9 (CH_3), 2.6 (CH_2), -1.6 (CH_3), -1.8 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3447, 2931, 2858, 1703, 1634, 1105; **HRMS** (ESI) *m/z* calcd for $C_{35}H_{55}INO_5Si_2$ [M+NH$_4$]$^+$ 752.2658, found 752.2659.

Minor diastereoisomer 200: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4H, Ar**H**), 7.46 – 7.33 (m, 6H, Ar**H**), 6.48 – 6.44 (m, 1H, C=C**H**), 4.60 (dd, $J_{AB, AX}$ = 18.4, 1.9 Hz, 1H, C**H**$_2$OSi), 4.41 (dd, $J_{BA, BX}$ = 18.3, 1.6 Hz, 1H, C**H**$_2$OSi), 3.76 – 3.64 (m, 3H, OC**H**$_2$C**H**$_2$O), 3.61 (d, J_{AB} = 9.3 Hz, 1H, C**H**$_2$I), 3.52 – 3.44 (m, 1H, OCH$_2$C**H**$_2$O), 3.12 (d, J_{BA} = 9.3 Hz, 1H, C**H**$_2$I), 1.86 – 1.80 (m, 1H, C**H**$_2$), 1.79 – 1.70 (m, 2H, C**H**$_2$), 1.57 – 1.49 (m, 1H, C**H**$_2$), 1.28 (s, 3H, C**H**$_3$CCH$_2$), 1.10 (s, 9H, CH$_2$OSiC(C**H**$_3$)$_3$), 0.78 (s, 9H, COSiC(C**H**$_3$)$_3$), 0.06 (s, 3H, SiC**H**$_3$), -0.16 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 204.9 (q), 179.3 (q), 135.6 (CH), 133.0 (q), 132.6 (q), 130.2 (CH), 130.1 (CH), 128.1 (CH), 128.1 (CH), 88.5 (q), 83.3 (q), 66.3 (q), 64.8 (CH_2), 62.1 (CH_2),

61.5 (CH_2), 36.2 (CH_2), 36.1 (CH_2), 26.9 (CH_3), 26.0 (CH_3), 19.4 (q), 19.1 (CH_3), 18.7 (q), 2.0 (CH_2), -1.2 (CH_3), -2.1 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3449, 2931, 2858, 1700, 1635, 1105; **HRMS** (ESI) *m/z* calcd for $C_{35}H_{52}IO_5Si_2$ $[M+H]^+$ 735.2392, found 735.2385.

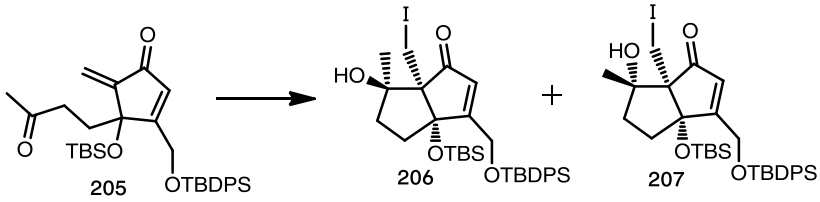
4-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-5-methylene-4-(3-oxobutyl)cyclopent-2-enone **205**

Exo-methylene **184** was dissolved in a solvent mixture of MeCN:H_2O (23 mL, 9:1) and DDQ (150 mg, 0.66 mmol, 0.2 equiv) was added in one portion. The reaction mixture was stirred at 40 °C for 4 hr before adding excess brine. The mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO2, hexane/EtOAc 17:3) afforded ketone **205** as a white solid (1.7 g, 92% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H, Ar**H**), 7.48 – 7.36 (m, 6H, Ar**H**), 6.66 (s, 1H, C=C**H**), 6.17 (s, 1H, C**H**$_2$=C), 5.49 (s, 1H, C**H**$_2$=C), 4.66 (dd, $J_{AB,\,AX}$ = 18.8, 1.7 Hz, 1H, C**H**$_2$OSi), 4.37 (dd, $J_{BA,\,BX}$ = 18.8, 1.8 Hz, 1H, C**H**$_2$OSi), 2.16 – 2.00 (m, 2H, C**H**$_2$), 1.98 (s, 3H, C**H**$_3$CO), 1.91 – 1.80 (m, 2H, C**H**$_2$), 1.09 (s, 9H, $CH_2OSiC(CH_3)_3$), 0.74 (s, 9H, $COSiC(CH_3)_3$), -0.08 (s, 3H, $SiCH_3$), -0.16 (s, 3H, $SiCH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.8 (q), 193.2 (q), 177.4 (q), 148.1 (q), 135.6 (CH), 135.5 (CH), 132.7 (q), 132.6 (q), 130.4 (CH), 130.2 (CH), 128.1 (CH), 128.0 (CH), 117.7 (CH_2), 79.5 (q), 60.1 (CH_2), 38.2 (CH_2), 33.0 (CH_2), 30.1 (CH_3), 26.9 (CH_3), 25.7 (CH_3), 19.4 (q), 18.3 (q), -2.5 (CH_3), -3.3 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2930, 2251, 1700, 1656, 1115; **Elemental Analysis** (%, w/w) calcd

for $C_{33}H_{46}O_4Si_2$ C(70.4), H(8.24), found C(70.4), H(8.24); **HRMS** (ESI) *m/z* calcd for $C_{33}H_{50}NO_4Si_2$ $[M+NH_4]^+$ 580.3273, found 580.3273; **MP** 78-80 °C.

3a-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-6-hydroxy-6a-(iodomethyl)-6-methyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one **206** and **207**

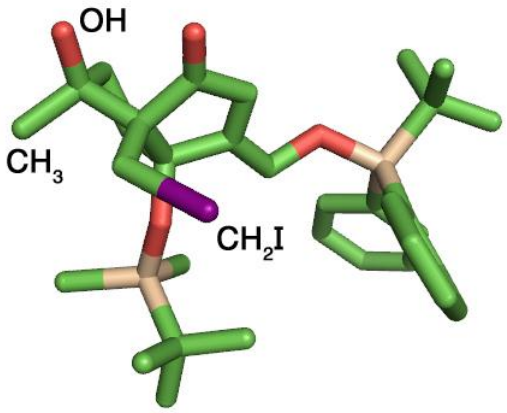


TBAI (1.31 g, 3.55 mmol, 2 equiv) was dissolved in dry DCM (20 mL) under N_2, cooled to 0 °C and left to stir for 10 mins. $TiCl_4$ (7.11 mL, 1 M in DCM, 7.11 mmol, 4 equiv) was added dropwise over a period of 10 mins to the cooled mixture and the resulting dark-red solution was left to stir for a further 5 mins before being warmed to RT. To the reaction mixture was added slowly a solution of ketone **205** (1 g, 1.78 mmol, 1 equiv) in dry DCM (10 mL) over 15 mins. The reaction was left to stir for a further 1 hr at which time the reaction was quenched with saturated NH_4Cl aqueous solution (15 mL). This was poured into a separating funnel and the organic phase was washed with brine and the aqueous phases were combined and re-extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure to leave a crude mixture which was further purified by flash column chromatography (SiO_2, Hexane/EtOAc, 9:1) which afforded a separable diastereomeric mixture of **206**:**207** (6:1) (d.r calculated from ^{1}H-NMR of crude). Major diastereomer **206** was obtained as a white solid (733 mg, 60% yield) and minor diastereomer **207** as a white solid (125 mg, 10% yield) and unreacted starting material **205** (250 mg). Minor diastereomer **207** (125 mg) was dissolved in DCM (5 mL), treated with basic alumina (1 g) in DCM and stirred overnight. All minor **207** was recycled back to starting material **205** (via a retro-aldol

process) as determined by ^{1}H-NMR of the crude reaction mixture. The stocks of unreacted starting material **205** were combined (330 mg, 0.59 mmol) and resubmitted again to the reaction conditions. After a single attempt of recycling, the combined overall yield of major diastereomer **206** was increased (936 mg, 79% combined yield) with a diminished quantity of minor diastereomer **207** (55 mg, 5% combined yield) in an isolated diastereomeric ratio of **206**:**207** (15:1).

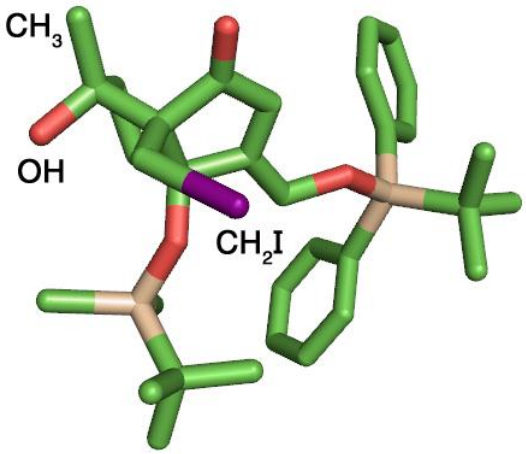
Major diastereoisomer 206: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4H, Ar**H**), 7.47 – 7.33 (m, 6H, Ar**H**), 6.52 (s, 1H, C=C**H**), 4.66 (d, *J* = 18.8 Hz, 1H, C**H**$_2$OSi), 4.63 (s, 1H, O**H**), 4.41 (d, *J* = 18.8 Hz, 1H, C**H**$_2$OSi), 3.49 (d, *J* = 9.6 Hz, 1H, C**H**$_2$I), 3.14 (d, *J* = 9.6 Hz, 1H, C**H**$_2$I), 1.83 – 1.69 (m, 3H, C**H**$_2$, C**H**$_2$), 1.41 – 1.29 (m, 1H, C**H**$_2$), 1.21 (s, 3H, C**H**$_3$CCH$_2$), 1.11 (s, 9H, CH$_2$OSiC(C**H**$_3$)$_3$), 0.76 (s, 9H, COSiC(C**H**$_3$)$_3$), 0.08 (s, 3H, SiC**H**$_3$), -0.17 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.7 (q), 182.6 (q), 135.6 (CH), 132.9 (q), 132.5 (q), 130.2 (CH), 130.2 (CH), 128.1(CH), 128.1 (CH), 127.1 (CH), 87.5 (q), 79.4 (q), 64.2 (q), 61.7 (CH_2), 39.1 (CH_2), 36.6 (CH_2), 26.9 (CH_3), 25.9 (CH_3), 22.6 (CH_3), 19.4 (q), 18.7 (q), 0.9 (CH_2), -1.1 (CH_3), -2.2 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3420, 2957, 2251, 1693, 1633; **Elemental Analysis** (%, w/w) calcd for $C_{33}H_{47}IO_4Si_2$ C(57.4), H(6.86), found C(57.6), H(6.91); **HRMS** (ESI) *m/z* calcd for $C_{33}H_{47}IO_4Si_2$ $[M+H]^+$, 691.2130, found 691.2134; **MP** 102-104 °C.

X-ray crystal structure for **206**:

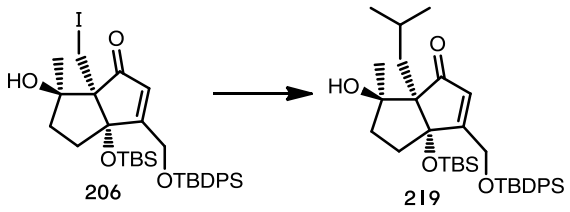


Minor diastereoisomer 207: **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H, Ar**H**), 7.46 – 7.34 (m, 6H, Ar**H**), 6.37 (t, J = 1.7 Hz, 1H, C=C**H**), 4.68 (dd, $J_{AB, AX}$ = 18.5, 1.9 Hz, 1H, C**H**$_2$OSi), 4.45 (dd, $J_{BA, BX}$ = 18.5, 1.7 Hz, 1H, C**H**$_2$OSi), 3.45 (d, J = 9.7 Hz, 1H, C**H**$_2$I), 3.26 (d, J = 9.7 Hz, 1H, C**H**$_2$I), 2.22 (td, J = 12.8, 6.7 Hz, 1H, C**H**$_2$), 1.72 (dd, J = 12.6, 6.6 Hz, 1H, C**H**$_2$), 1.65 (dd, J = 13.4, 6.6 Hz, 1H, C**H**$_2$), 1.43 (s, 3H, C**H**$_3$CCH$_2$), 1.25 (td, J = 13.2, 6.7 Hz, 1H, CH$_3$C**H**$_2$CH$_2$), 1.11 (s, 9H, CH$_2$OSiC(C**H**$_3$)$_3$), 0.78 (s, 9H, COSiC(C**H**$_3$)$_3$), 0.10 (s, 3H, SiC**H**$_3$), -0.12 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (176 MHz, $CDCl_3$) δ 205.4 (q), 180.5 (q), 135.6 (CH), 133.2 (CH), 132.7 (CH), 130.1 (CH), 130.1 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 89.9 (q), 80.8 (q), 66.9 (q), 61.7 (CH_2), 38.5 (CH_2), 35.8 (CH_2), 27.0 (CH_3), 26.0 (CH_3), 23.9 (CH_3), 19.4 (q), 18.6 (q), 1.8 ((CH_2), -2.1 (CH_3), -2.2 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3449, 2930, 2251, 1693, 1632; **HRMS** (ESI) *m/z* calcd for $C_{33}H_{47}IO_4Si_2$ [M+H]$^+$, 691.2130, found 691.2131; **MP** 106-108 °C.

X-ray crystal structure for **207**:



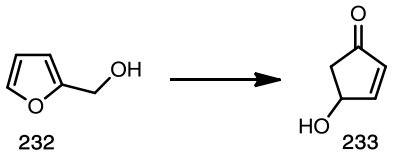
(3aS,6R,6aR)-3a-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-6-hydroxy-6a-isobutyl-6-methyl-4,5,6,6a-tetrahydropentalen-1(3aH)-one **219**



Bicycle **206** (30 mg, 0.04 mmol, 1 equiv) was dissolved in anhydrous THF (2 mL) and cooled to 0 °C before dropwise addition isopropylmagnesium chloride lithium chloride (0.1 mL, 1.3 M in THF, 0.13 mmol, 3 equiv). The reaction mixture was stirred for 30 mins at 0 °C before quenching with brine, extracted with DCM, dried over $MgSO_4$ filtered and solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) afforded the title compound **219** as a colourless oil (26 mg, 98% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 4H, Ar**H**), 7.47 – 7.34 (m, 6H, Ar**H**), 6.46 (s, 1H, C=C**H**), 5.14 (s, 1H, O**H**), 4.64 (dd, $J_{AB, AX}$ = 18.7, 1.6 Hz, 1H, C**H**$_2$OSi), 4.44 (dd, $J_{BA, BX}$ = 18.7, 1.6 Hz, 1H, C**H**$_2$OSi), 1.79 – 1.62 (m, 1H, C**H**$_2$), 1.60 – 1.50 (m, 3H, C**H**$_2$, C**H**$_2$), 1.18 (s, 3H, C**H**$_3$CCH$_2$), 1.10 (s, 9H, CH$_2$OSiC(C**H**$_3$)$_3$), 0.84 (d, J = 6.7 Hz, 3H, C**H**$_3$CH), 0.82 (d, J = 6.5 Hz, 3H, C**H**$_3$CH), 0.71 (s, 9H, COSiC(C**H**$_3$)$_3$), 0.07 (s, 3H, SiC**H**$_3$), -0.18 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 213.2 (q), 183.3 (q), 135.5 (CH), 135.5 (CH), 132.8 (q), 132.6 (q), 130.2 (CH), 128.1 (CH), 88.1 (q), 79.0 (q), 66.0 (q), 61.8 (CH_2), 38.5 (CH_2), 37.8 (CH_2), 36.6 (CH_2), 26.9 (CH_3), 26.0 (CH_3), 25.7 (CH_3), 24.2 (CH) 24.2 (CH_3), 22.9 (CH_3), 19.4 (q), 18.6 (q), -1.1 (CH_3), -1.9 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3446, 2956, 1683, 1632, 1471, 1113; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{54}O_4Si_2Na$ $[M+Na]^+$, 629.3453, found 629.3459.

4-Hydroxycyclopent-2-enone **233**



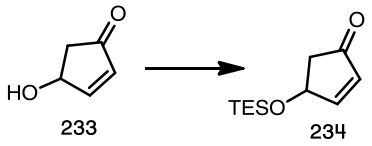
232 233

Furfuryl alcohol **232** (15 g, 153 mmol, 1 equiv) was dissolved in deionised water (500 mL) and the resulting solution was deoxygenated with a stream of N_2 for 1 hr. Following addition of hydroquinone (160 mg, 1.45 mmol, 0.0095 equiv) and sodium dihydrogenphosphate (734 mg, 6.1 mmol, 0.04 equiv), the pH was adjusted to 4.1 by careful addition of 0.25 M orthophosphoric acid and the reaction mixture was then heated to reflux for 24 hr. Formation of a thick brown oil was observed, which was dispersed by addition of 1,4-dioxane (200 mL) before returning the mixture to reflux for a further 48 hr. After cooling to RT, the solution was washed with toluene and the aqueous layer was concentrated *in vacuo* to approximately 200 mL. Azeotropic distillation under reduced pressure with ethanol to remove the remaining water left a dark brown oil. The crude was diluted with EtOAc, dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Flash column chromatography (SiO_2, EtOAc) furnished cyclopentenol **233** as an orange oil (8.98 g, 60% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, $J_{AB,\,AX}$ = 5.6, 2.2 Hz, 1H, CHC**H**=CH), 6.16 (d, J = 5.6 Hz, 1H, CHCH=C**H**), 4.99 (d, J = 4.5 Hz, 1H, C**H**OH), 3.50 (s, 1H, CHO**H**), 2.71 (dd, $J_{AB,\,AX}$ = 18.5, 6.0 Hz, 1H, C**H**$_2$), 2.23 (dd, $J_{BA,\,BX}$ = 18.5, 1.9 Hz, 1H, C**H**$_2$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 207.5 (q), 164.1 (CH), 134.9 (CH), 70.3 (CH), 44.3 (CH_2).

The spectroscopic data were in agreement with those previously published.[90]

4-(Triethylsilyloxy)cyclopent-2-enone **234**

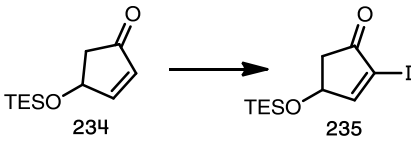


A solution of cyclopentenol **233** (15.2 g, 155 mmol, 1 equiv), triethylamine (59.3 mL, 423 mmol, 2.73 equiv) and DMAP (1.9 g, 15 .5 mmol, 0.1 equiv) in anhydrous DCM (160 mL) and was stirred at RT for 10 mins under an atmosphere of N_2. This mixture was then cooled to 0°C at which time TESCl (25.7 g, 171 mmol, 1.1 equiv) was slowly added to the reaction mixture and left for 3 hr at RT. The reaction mixture was poured into a separating funnel containing saturated NH_4Cl solution, extracted with DCM and the organic layer washed with brine, dried over $MgSO_4$ and evaporated to dryness. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished **234** as a clear pale yellow oil (26.3 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, $J_{AB, AX}$ = 5.7, 2.3 Hz, 1H, CHC**H**=CH), 6.18 (dd, $J_{BA, BX}$ = 5.6, 1.3 Hz, 1H, CHCH=C**H**), 5.01 – 4.95 (m, 1H, C**H**OSi), 2.71 (dd, $J_{AB, AX}$ = 18.2, 6.0 Hz, 1H, C**H**$_2$CO), 2.26 (dd, $J_{BA, BX}$ = 18.2, 2.2 Hz, 1H, C**H**$_2$CO), 1.03 – 0.93 (m, 9H, Si(CH_2C**H**$_3$)$_3$), 0.70 – 0.55 (m, 6H, Si(C**H**$_2$$CH_3$)$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.5 (q), 163.9 (CH), 134.6 (CH), 70.6 (CH), 45.1 (CH_2), 6.7 (CH_3), 4.8 (CH_2).

The spectroscopic data were in agreement with those previously published.[91]

2-iodo-4-(triethylsilyloxy)cyclopent-2-enone **235**

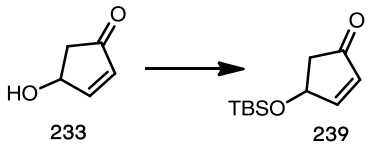


Enone **234** (17.7g, 83 mmol, 1 equiv) was dissolved in a solvent mixture of DCM:pyridine (125 mL, 1:1.5) and stirred for 10 mins before iodine (63.8 g, 250 mmol, 3 equiv) was added in one portion. The reaction mixture was left stirring at RT for 2 hr before being poured into a separating funnel containing saturated sodium thiosulfate, extracted with DCM and the organic layer washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 19:1) afforded α-iodo enone **235** as a yellow oil (16.1 g, 57% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 2.5 Hz, 1H, C**H**=CI), 4.93 (dt, J = 6.0, 2.3 Hz, 1H, C**H**OSi), 2.85 (dd, $J_{AB, AX}$ = 18.2, 6.1 Hz, 1H, CH_2CO), 2.34 (dd, $J_{BA, BX}$ = 18.2, 2.1 Hz, 1H, CH_2CO), 0.96 (t, J = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$), 0.63 (q, J = 7.9 Hz, 6H, Si(C$H_2$$CH_3$)$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.2 (q), 169.2 (CH), 105.0 (q), 71.9 (CH), 42.5 (CH_2), 6.7 (CH_3), 4.8 (CH_2).

The spectroscopic data were in agreement with those previously published.[141]

4-(*tert*-Butyldimethylsilyloxy)cyclopent-2-enone **239**



A solution of cyclopentenol **233** (6.2 g, 63 mmol, 1 equiv), triethylamine (20.2 mL, 145 mmol, 2.3 equiv) and DMAP (772 mg, 6.3 mmol, 0.1 equiv) in DCM (40 mL) was stirred for 10 mins at 0 °C before addition of TBSCl (10.5 g, 70 mmol, 1.1

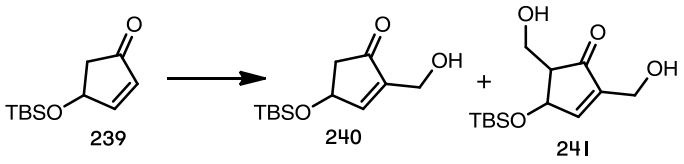
equiv). The resulting mixture was then heated to reflux for 2 hr before addition of saturated NH_4Cl solution. After separation of the organic layer, the aqueous phase was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 9:1) yielded cyclopentenone **239** as orange needlelike crystals (11.39 g, 85% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45 (dd, $J_{AB, AX}$ = 5.6, 2.2 Hz, 1H, CHC**H**=CH), 6.18 (dd, $J_{BA, BX}$= 5.6, 1.1 Hz, 1H, CHCH=C**H**), 5.04 – 4.95 (m, 1H, C**H**OSi), 2.71 (dd, $J_{AB, AX}$ = 18.2, 6.0 Hz, 1H, C**H**$_2$CO), 2.24 (dd, $J_{BA, BX}$ = 18.2, 2.2 Hz, 1H, C**H**$_2$CO), 0.91 (s, 9H, Si(C**H**$_3$)$_3$), 0.16 – 0.10 (m, 6H, 2 × SiC**H**$_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.5 (q), 163.9 (CH), 134.5 (CH), 71.0 (CH), 45.1 (CH_2), 25.8 (CH_3), 18.2 (q), -4.6 (CH_3), -4.6 (CH_3) ; **MP** 30-32 °C

The spectroscopic data were in agreement with those previously published.[142]

4-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)cyclopent-2-enone **240** and

4-(*tert*-Butyldimethylsilyloxy)-2,5-bis(hydroxymethyl)cyclopent-2-enone **241**



A solution of cyclopentenone **239** (5 g, 24 mmol, 1 equiv), imidazole (802 mg, 11.8 mmol, 0.5 equiv), formaldehyde (9.65 mL, 37% Aq solution, 130 mmol, 5.5 equiv) in THF:H_2O (48 mL, 1:1) was stirred at RT for six days before addition of EtOAc. The organic layer was separated and the aqueous layer was extracted twice with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Flash column chromatography (SiO_2,

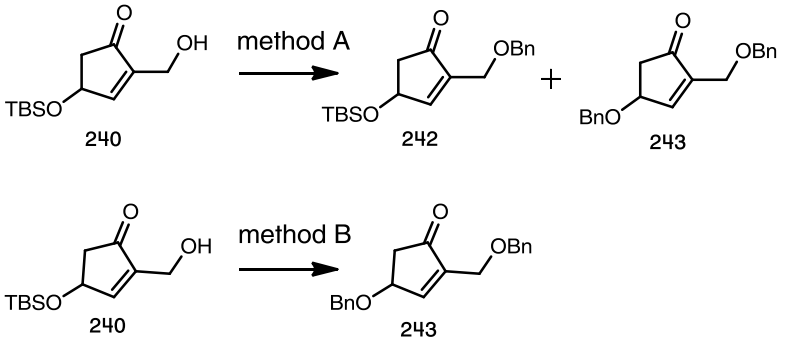
hexane/EtOAc 7:3) yielded a separable mixture of products, alcohol **240** (2.28 g, 40% yield) and diol **241** (0.63 g, 11% yield), both as colourless oils.

Alcohol 240: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H, C**H**=C), 4.96 – 4.91 (m, 1H, C**H**CH=C), 4.43 – 4.31 (m, 2H, C**H$_2$**OH), 2.78 (dd, *J* = 18.4, 5.9 Hz, 1H, C**H$_2$**CO), 2.38 – 2.27 (m, 2H, C**H$_2$**CO, O**H**), 0.90 (s, 9H, Si(C**H$_3$**)$_3$), 0.15 – 0.10 (m, 6H, **2** × SiC**H$_3$**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.1 (q), 157.6 (CH), 145.6 (q), 69.2 (CH), 57.5 (CH_2), 46.0 (CH_2), 25.9 (CH_3), 18.2 (q), -4.6 (CH_3), -4.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3435, 2930, 1710, 1471, 1254, 1088; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{23}O_3Si$ $[M+H]^+$, 243.1411, found 243.1412.

Diol 241: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 1H, C**H**=C), 4.88 – 4.82 (m, 1H, C**H**CH=C), 4.45 – 4.32 (m, 2H, CC**H$_2$**OH), 4.15 – 4.06 (m, 1H, CHC**H$_2$**OH), 3.90 – 3.81 (m, 1H, CHC**H$_2$**OH), 2.53 – 2.46 (m, 1H, C**H**CH$_2$OH), 2.26 – 2.09 (m, 2H, 2 × O**H**), 0.91 (s, 9H, Si(C**H$_3$**)$_3$), 0.17 – 0.14 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.8 (q), 157.8 (CH), 145.3 (q), 71.7 (CH), 59.4 (CH_2), 58.9 (CH), 57.4 (CH_2), 25.9 (CH_3), 18.2 (q), -4.5 (CH_3), -4.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3334, 2929, 2250, 1712, 1464, 1259, 1080; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{28}NO_4Si$ $[M+NH_4]^+$, 290.1782, found 290.1783; **MP** 68-70 °C.

2-(Benzyloxymethyl)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone **242**

and 4-(benzyloxy)-2-(benzyloxymethyl)cyclopent-2-enone **243**



Method A: A mixture of alcohol **240** (100 mg, 0.41 mmol, 1 equiv), 2-benzyloxy-1-methylpyridinium triflate (303 mg, 0.87 mmol, 2.1 equiv) and MgO (34.9 mg, 0.7 mmol, 2.1 equiv, vacuum dried) were dissolved in benzotrifluoride (0.85 mL) and heated to 85 °C for 22 hr. The reaction mixture was cooled to RT and excess saturated NH_4Cl was added. The resulting mixture was extracted with EtOAc, the organic phase washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) afforded a separable mixture of mono-benzylated **242** as a colourless oil (20 mg, 15% yield) and *bis*-benzylated **243** as a colourless oil (63 mg, 50% yield).

Method B: A solution of alcohol **240** (50 mg, 0.21 mmol, 1 equiv), benzyl trichloroacetimidate (104 mg, 0.41 mmol, 2 equiv) and triflic acid (10 µL, 0.11 mmol, 0.54 equiv) were dissolved in a solvent mixture of cyclohexane:DCM (5 mL, 2:1) and stirred at RT for 4 hr. The reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl, brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished *bis*-benzylated **243** as a colourless oil (9.9 mg, 16% yield).

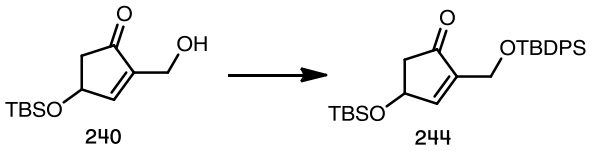
***Mono*-benzylated 242: ^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H, **6** × Ar**H**, 1 × C**H**=C), 4.97 – 4.89 (m, 1H, C**H**CH=C), 4.58 (s, 2H, OC**H$_2$**Ph), 4.23 – 4.18 (m, 2H, C**H$_2$**OBn), 2.77 (dd, $J_{AB,\,AX}$ = 18.3, 5.9 Hz, 1H, C**H$_2$**CO), 2.32 (dd, $J_{BA,\,BX}$ = 18.3, 2.1

Hz, 1H, CH_2CO), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.16 – 0.09 (m, 6H, 2 × $SiCH_3$); **^{13}C NMR** (91 MHz, $CDCl_3$) δ 204.9 (q), 158.3 (CH), 144.2 (q), 137.9 (q), 128.6 (CH), 128.0 (CH), 127.9 (CH), 73.5 (CH_2), 69.3 (CH), 64.0 (CH_2), 45.9 (CH_2), 25.9 (CH_3), 18.3 (q), -4.6 (CH_3), -4.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2929, 1713, 1471, 1362, 1254, 1089; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{29}O_3Si$ $[M+H]^+$, 333.1880, found 333.1880.

***Bis*-benzylated 243: ^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 1H, C**H**=C), 7.43 – 7.27 (m, 10H, Ar**H**), 4.75 – 4.70 (m, 1H, C**H**OBn), 4.67 – 4.55 (m, 4H, 2 × C**H$_2$**Ph), 4.27 – 4.19 (m, 2H, C**H$_2$**O), 2.75 (dd, $J_{AB,\,AX}$ = 18.3, 5.9 Hz, 1H, CH_2CO), 2.45 (dd, $J_{BA,\,BX}$ = 18.3, 2.0 Hz, 1H, CH_2CO); **^{13}C NMR** (201 MHz, $CDCl_3$) δ 204.4 (q), 155.4 (CH), 145.6 (q), 137.9 (q), 137.7 (q), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 75.2 (CH), 73.4 (CH_2), 71.9 (CH_2), 64.0 (CH_2), 42.7 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3030, 2858, 2250, 1710, 1496, 1454, 1094; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{21}O_3$ $[M+H]^+$, 309.1485, found 309.1489.

4-(*tert*-Butyldimethylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)cyclopent-2-enone

244

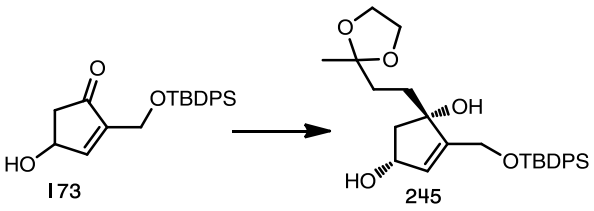


A solution of alcohol **240** (6.8 g, 28.1 mmol, 1 equiv), imidazole (4.77 g, 70.1 mmol, 2.5 equiv) and DMAP (343 mg, 2.8 mmol, 0.1 equiv) in DMF (50 mL) was stirred for 10 mins at 0 °C before addition of TBDPSCl (9.25 g, 33.7 mmol, 1.2 equiv). The resulting mixture was then allowed to warm to RT and stirred for 2 hr before being quenched with H_2O (5 mL) and poured into a separating funnel containing Et_2O and distilled H_2O. The organic layer was separated and washed twice with distilled water to remove any residual DMF. The organic extract was dried over $MgSO_4$, filtered

and solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) yielded cyclopentenone **244** as a pale yellow oil (9.98 g, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H, Ar**H**), 7.47 – 7.35 (m, 7H, **6** × Ar**H,** 1 × CHC**H**=C), 4.97 – 4.91 (m, 1H, C**H**CH=C), 4.47 – 4.41 (m, 2H, C**H$_2$**O), 2.76 (dd, *J* = 18.3, 5.9 Hz, 1H, C**H$_2$**CO), 2.32 (dd, *J* = 18.3, 1.9 Hz, 1H, C**H$_2$**CO), 1.10 (s, 9H, $CH_2OSiC(CH_3)_3$), 0.94 (s, 9H, $COSiC(CH_3)_3$), 0.17 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 204.7 (q), 157.1 (CH), 146.9 (q), 135.6 (CH), 135.6 (CH), 133.2 (q), 133.1 (q), 130.0 (CH), 130.0 (CH), 127.9 (CH), 69.2 (CH), 58.9 (CH_2), 46.3 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 19.4 (q), 18.3 (q), -4.5 (CH_3), -4.5 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3071, 2930, 1713, 1471, 1428, 1254, 1113; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{44}NO_3Si_2$ $[M+Na]^+$, 498.2854, found 498.2851.

5-((*tert*-Butyldiphenylsilyloxy)methyl)-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-4-ene-1,3-diol **245**

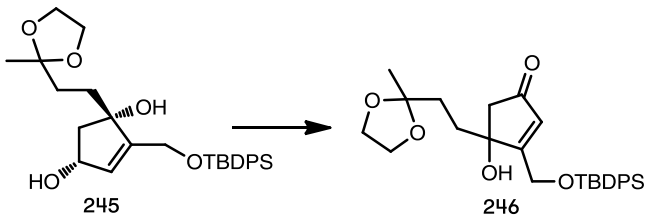


Iodo-dioxolane **147** (13.2 g, 55 mmol, 4 equiv) was dissolved in dry Et_2O (100 mL), cooled to –78 °C under an atmosphere of N_2 before slow addition of ^{t}BuLi (67.6 mL, 1.7 M solution in pentane, 115 mmol, 8.4 equiv). The resulting mixture was stirred at –78 °C for 45 mins before warming to room temperature and stirring for another 1 hr. At which time, the mixture was cannulated into a precooled solution of enone **173** (5 g, 13.6 mmol, 1 equiv) in dry Et_2O (50 mL) at –78°C. The resulting reaction mixture was stirred at –78 °C for 1.5 hr before warming to room temperature and left for a further 30 mins. The reaction was quenched with distilled water (10 mL) and poured into a separating funnel containing saturated NH_4Cl solution. The organic

layer was separated and the aqueous fraction was extracted twice with EtOAc. The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Purification by flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished an inseparable 6:1 diastereomeric mixture of tertiary alcohol **245** as an oil (4.73 g, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) **major diastereomer**: δ 7.74 – 7.65 (m, 4H, Ar**H**), 7.47 – 7.36 (m, 7H, 6 × Ar**H**, 1 × C**H**=C), 5.85 – 5.82 (m, 1H), 4.57 (s, 1H, C**H**OH), 4.46 – 4.28 (m, 2H, C**H$_2$**O), 3.98 – 3.80 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.96 (s, 1H, O**H**), 2.42 (dd, $J_{AB,\,AX}$ = 14.2, 6.9 Hz, 1H, C**H$_2$**COH), 1.98 – 1.64 (m, 3H, C**H$_2$**, C**H$_2$**COH), 1.60 – 1.45 (m, 2H, C**H$_2$**), 1.27 (s, 3H, C**H$_3$**CCH_2), 1.07 (s, 9H, SiC(C**H$_3$**)$_3$); The ^{1}H NMR signals of the minor diastereoisomer were too weak to be confidently assigned; **^{13}C NMR** (126 MHz, $CDCl_3$) **major diastereomer**: δ 149.6 (q), 135.7 (CH), 135.6 (CH), 132.9 (q), 132.8 (q), 130.6 (CH), 130.0 (CH), 129.9 (CH), 127.8 (CH), 127.8 (CH), 109.8 (q), 83.7 (q), 73.5 (CH), 64.7 (CH_2), 60.8 (CH_2), 48.2 (CH_2), 33.7 (CH_2), 32.7 (CH_2), 26.8 (CH_3), 23.9 (CH_3), 19.1 (q); The ^{13}C NMR signals of the minor diastereoisomer were too weak to be confidently assigned; **IR** (thin film, NaCl plate, cm^{-1}) 3398, 2932, 2247, 1472, 1428, 1113; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{42}NO_5Si$ $[M+NH_4]^+$, 500.2827, found 500.2823.

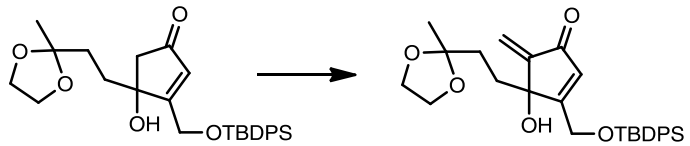
3-((*tert*-Butyldiphenylsilyloxy)methyl)-4-hydroxy-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone **246**



A solution of tertiary alcohol **245** (1 g, 2.07 mmol, 1 equiv), $NaHCO_3$ (0.87 g, 10.36 mmol, 5 equiv) and DMP (1.14 g, 2.69 mmol, 1.3 equiv) in DCM (30 mL) was stirred at RT for 1 hr. The reaction mixture was quenched with H_2O (5 mL) and the organic layer was separated, washed with brine, dried over $MgSO_4$ filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexane/EtOAc 4:6) furnished enone **246** as an off-white solid (0.92 g, 92 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 4H, Ar**H**), 7.49 – 7.34 (m, 6H, Ar**H**), 6.21 (t, J = 1.7 Hz, 1H, C=C**H**), 4.69 (dd, $J_{AB, AX}$ = 17.5, 1.8 Hz, 1H, C**H**$_2$OH), 4.54 (dd, $J_{BA, BX}$ = 17.5, 1.6 Hz, 1H, C**H**$_2$OH), 4.01 – 3.76 (m, 4H, OC**H**$_2$C**H**$_2$O), 2.97 (s, 1H, O**H**), 2.60 (d, J = 18.3 Hz, 1H, C**H**$_2$CO), 2.48 (d, J = 18.3 Hz, 1H, C**H**$_2$CO), 1.95 – 1.84 (m, 1H, C**H**$_2$), 1.80 – 1.67 (m, 1H, C**H**$_2$), 1.66 – 1.49 (m, 2H, C**H**$_2$), 1.26 (s, 3H, C**H**$_3$CCH$_2$), 1.08 (s, 9H, SiC(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.7 (q), 179.8 (q), 135.7 (CH), 135.6 (CH), 132.5 (q), 132.5 (q), 130.3 (CH), 130.2 (CH), 129.1 (CH), 128.1 (CH), 109.5 (q), 79.2 (q), 64.8 (CH_2), 64.8 (CH_2), 60.9 (CH_2), 50.1 (CH_2), 34.0 (CH_2), 32.9 (CH_2), 26.9 (CH_3), 24.0 (CH_3), 19.3 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3425, 2932, 2249, 1695, 1628, 1114; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{36}O_5SiNa$ $[M+Na]^+$, 503.2224, found 503.2229; **MP** 60-62 °C.

3-((*tert*-Butyldiphenylsilyloxy)methyl)-4-hydroxy-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-methylenecyclopent-2-enone **247**



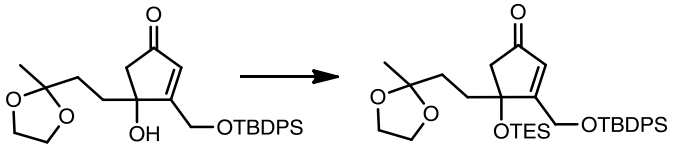
246 247

A solution of enone **246** (750 mg, 1.56 mmol, 1 equiv) in anhydrous THF (20 mL) was cooled to –78 °C under N_2 and stirred for 10 mins before slow addition of LDA (4.33 mL, 1.8 M solution in THF/heptane/ethylbenzene, 7.80 mmol, 5 equiv). The reaction mixture was stirred for 1 hr and then cannulated across to a precooled solution of Eschenmoser's salt (808 mg, 4.68 mmol, 4 equiv) in THF (10 mL) at –78 °C. The reaction was left stirring at –78 °C for 2 hr before allowing to warm to RT and stirred for a further 30 mins. The reaction was quenched with a saturated $NaHCO_s$ solution and extracted with DCM. The DCM extracts were washed with brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. The crude orange residue was dissolved in a mixture of DCM:$NaHCO_3$ (30 mL, 2:1) and under vigorous stirring, one portion of *m*CPBA (808 mg, 4.68 mmol, 3 equiv) was carefully added and left to stir for 1 hr before separating the organic layer. The aqueous layer was extracted with DCM and the combined organic fractions were dried over $MgSO_4$, filtered and solvent removed under reduced pressure leaving an orange crude oil. Flash column chromatography (SiO_2, hexane/EtOAc 4:6) afforded an inseparable 2:1 mixture of *exo*-methylene **247** (ca. 209 mg, 27% yield) and starting material **246** (ca. 113 mg, 33%) as an impure white solid (322 mg) as determined by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.59 (m, 4H, Ar**H**), 7.49 – 7.34 (m, 6H, Ar**H**), 6.56 (s, 1H, C=C**H**), 6.09 (s, 1H, C**H**$_2$=C), 5.56 (s, 1H, C**H**$_2$=C), 4.72 (dd, *J* = 18.5, 1.8 Hz, 1H, C**H**$_2$O), 4.54 (dd, *J* = 18.5, 1.8 Hz, 1H, C**H**$_2$O), 3.97 – 3.68 (m, 4H, OC**H**$_2$C**H**$_2$O), 2.20 (s, 1H, O**H**), 1.97 (td, *J* = 12.8, 4.6 Hz, 1H, $CH_3CCH_2CH_2$), 1.78 –

1.70 (m, 1H, $CH_3CCH_2CH_2$), 1.45 – 1.36 (m, 1H, $CH_3CCH_2CH_2$), 1.18 (s, 3H, CH_3CCH_2), 1.09 (s, 9H, $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.1 (q), 176.4 (q), 149.6 (q), 135.7 (CH), 135.6 (CH), 132.7 (q), 132.6 (q), 130.6 (CH), 130.3 (CH0, 130.2 (CH), 128.1 (CH), 128.1 (CH), 116.4 (CH_2), 109.3 (q), 78.6 (q), 64.8 (CH_2), 64.8 (CH_2), 60.4 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 26.9 (CH_3), 23.9 (CH_3), 19.4 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3415, 2932, 2249, 1700, 1114; **HRMS** (ESI) *m/z* calcd for $C_{29}H_{36}O_5SiNa$ $[M+Na]^+$, 515.2224, found 515.2217.

3-((*tert*-Butyldiphenylsilyloxy)methyl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-4-(triethylsilyloxy)cyclopent-2-enone **248**



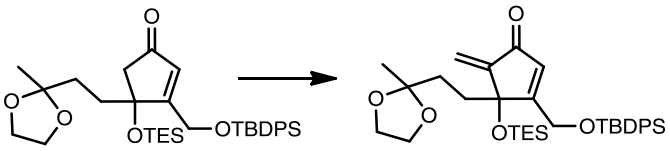
246 248

Tertiary alcohol **246** (2.1 g, 4.37 mmol, 1 equiv), 2,6-lutidine (3.2 mL, 27.53 mmol, 6.3 equiv) was dissolved in dry DMF (40 mL) and cooled to 0 °C under an atmosphere of N_2. The resulting mixture was stirred for 5 mins before dropwise addition of a TESOTf (2.96 mL, 13.11 mmol, 3 equiv). The reaction mixture was stirred for 20 mins before warming to RT and left for a further 1.5 hr until the reaction was complete as confirmed by TLC. This was then quenched with saturated NH_4Cl solution extracted with Et_2O. The Et_2O extracts was washed twice with distilled water to remove residual DMF and the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) supplied TES ether **248** as a colourless oil (2.28 g, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H, Ar**H**), 7.47 – 7.36 (m, 6H, Ar**H**), 6.37 (t, J = 1.9 Hz, 1H, C=C**H**), 4.64 (dd, $J_{AB, AX}$ = 18.7, 1.8 Hz, 1H, CH_2OH), 4.45 (dd, J = 18.7, 2.0 Hz, 1H, CH_2OH), 3.94 – 3.71 (m, 4H, OCH_2CH_2O), 2.56 (d, J = 1.9

Hz, 2H, C**H**$_2$CO), 1.84 – 1.74 (m, 1H, C**H**$_2$), 1.53 – 1.42 (m, 2H, CH$_3$CC**H**$_2$C**H**$_2$), 1.35 – 1.26 (m, 1H, C**H**$_2$), 1.20 (s, 3H, C**H**$_3$CCH$_2$), 1.08 (s, 9H, SiC(C**H**$_3$)$_3$), 0.82 (t, J = 7.9 Hz, 9H, , Si(CH$_2$C**H**$_3$)$_3$), 0.51 – 0.43 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.4 (q), 182.7 (q), 135.6 (CH), 135.6 (CH), 133.0 (q), 132.9 (q), 130.1 (CH), 130.1 (CH), 128.3 (CH), 128.0 (CH), 128.0 (CH), 109.5 (q), 80.6 (q), 64.8 (CH_2), 64.8 (CH_2), 60.4 (CH_2), 50.2 (CH_2), 34.7 (CH_2), 34.1 (CH_2), 26.9 (CH_3), 24.0 (CH_3), 19.4 (q), 7.0 (CH_3), 6.3 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2956, 1719, 1631, 1428, 1244; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{54}NO_5Si_2$ $[M+NH_4]^+$, 612.3535, found 612.3524.

3-((*tert*-Butyldiphenylsilyloxy)methyl)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-methylene-4-(triethylsilyloxy)cyclopent-2-enone **249**



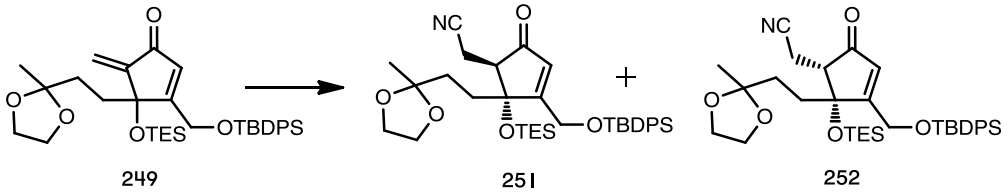
248 249

A solution of enone **248** (2.5 g, 4.20 mmol, 1 equiv) in anhydrous THF (65 mL) was cooled to –78 °C under N_2 and stirred for 10 mins before slow addition of LDA (7.01 mL, 1.8 M solution in THF/heptane/ethylbenzene, 12.61 mmol, 3 equiv). The reaction mixture was stirred for 1 hr and then cannulated across to a precooled solution of Eschenmoser's salt (2.33 g, 12.61 mmol, 3 equiv) in dry THF (30 mL) at –78 °C. The resulting solution was left stirring at –78 °C for 2 hr before allowing to warm to RT and stirred for a further 30 mins. The reaction was quenched with a saturated $NaHCO_3$ solution and extracted with DCM. The DCM extracts were washed with brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. The crude orange residue was dissolved in a mixture of DCM:$NaHCO_3$ (75 mL, 2:1) and under vigorous stirring, one portion of *m*CPBA (2.18 g, 12.61 mmol, 3 equiv) was carefully added and left to stir for 30 mins before

separating the organic layer. The aqueous layer was extracted with DCM and the combined organic fractions were dried over $MgSO_4$, filtered and solvent removed under reduced pressure leaving an orange crude oil. Flash column chromatography (SiO_2, hexane/EtOAc 17:3) afforded *exo*-methylene **249** as a white solid (2.17 g, 85 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 4H, Ar**H**), 7.49 – 7.35 (m, 6H, Ar**H**), 6.65 (s, 1H, C=C**H**), 6.14 (s, 1H, C**H**$_2$=C), 5.51 (s, 1H, C**H**$_2$=C), 4.63 (dd, $J_{AB,\ AX}$ = 19.0, 1.9 Hz, 1H, C**H**$_2$O), 4.47 (dd, $J_{BA,\ BX}$ = 19.0, 2.0 Hz, 1H, C**H**$_2$O), 3.88 – 3.68 (m, 4H, OC**H**$_2$C**H**$_2$O), 1.92 (td, J = 13.0, 4.3 Hz, 1H, $CH_3CCH_2CH_2$), 1.67 (td, J = 12.9, 4.2 Hz, 1H, $CH_3CCH_2CH_2$), 1.28 (td, J = 13.3, 4.4 Hz, 1H, $CH_3CCH_2CH_2$), 1.16 (s, J = 7.0 Hz, 3H, C**H**$_3$CCH$_2$), 1.14 – 1.03 (m, 10H, 9 × SiC(C**H**$_3$)$_3$, 1 × $CH_3CCH_2CH_2$), 0.79 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.51 – 0.29 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.6 (q), 178.1 (q), 148.7 (q), 135.6 (CH), 135.6 (CH), 132.8 (q), 132.8 (q), 130.1 (CH), 130.1 (CH), 130.0 (CH), 128.1 (CH), 128.0 (CH), 116.9 (CH_2), 109.4 (CH), 79.7 (q), 64.7 (CH_2), 64.7 (CH_2), 60.1 (CH_2), 34.0 (CH_2), 33.4 (CH_2), 26.9 (CH_3), 23.8 (CH_3), 19.4 (q), 7.0 (CH_3), 6.1 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2955, 1740, 1709, 1618, 1240, 1114; **HRMS** (ESI) *m/z* calcd for $C_{35}H_{54}NO_5Si_2$ $[M+NH_4]^+$, 624.3535, found 624.3540; **MP** 72-74 °C.

2-(3-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-oxo-2-(triethylsilyloxy)cyclopent-3-enyl)acetonitrile **251** and **252**



249 251 252

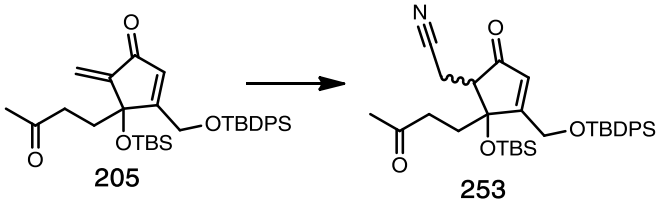
Exo-methylene **249** (100 mg, 0.165 mmol, 1 equiv) was dissolved in anhydrous DCM (8 mL) and cooled to 0 °C before the dropwise addition of diethylaluminium cyanide (198 µL µL, 1M solution in toluene, 0.198 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 1 hr before quenching with saturated $NaHCO_3$ solution (2 mL). The mixture was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 4:1) furnished a separable 1.1:1 diastereomeric mixture of **251** (36 mg, 35% yield) and **252** (32 mg, 31% yield), both as oils in a combined 66% overall yield.

Major diastereomer 251: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.57 (m, 4H, Ar**H**), 7.50 – 7.36 (m, 6H, Ar**H**), 6.48 (t, J = 1.7 Hz, 1H, C=C**H**), 4.63 (dd, $J_{AB,\,AX}$ = 18.8, 1.6 Hz, 1H, C**H**$_2$O), 4.36 (dd, $J_{BA,\,BX}$ = 18.9, 1.9 Hz, 1H, C**H**$_2$O), 3.99 – 3.79 (m, 4H, OC**H**$_2$C**H**$_2$O), 2.89 (dd, J = 8.0, 6.4 Hz, 1H, C**H**CH$_2$), 2.80 (dd, J = 17.3, 6.3 Hz, 1H, C**H**$_2$CN), 2.51 (dd, J = 17.3, 8.2 Hz, 1H, C**H**$_2$CN), 1.92 – 1.81 (m, 1H, CH$_3$CC**H**$_2$), 1.67 (td, J = 13.3, 5.9 Hz, 1H, CH$_3$CC**H**$_2$), 1.27 – 1.17 (m, 1H, CH$_3$CCH$_2$C**H**$_2$), 1.15 (s, 3H, C**H**$_3$CCH$_2$), 1.08 (s, 9H, SiC(C**H**$_3$)$_3$), 0.87 – 0.78 (m, 10H, 9 × Si(CH$_2$C**H**$_3$)$_3$), 1 × CH$_3$CCH$_2$C**H**$_2$), 0.49 (q, J = 7.9 Hz, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.1 (q), 180.8 (q), 135.6 (CH), 135.5 (CH), 132.6 (q), 132.5 (q), 130.2 (CH), 128.1 (CH), 126.8 (CH), 118.6 (q), 109.0 (q), 82.2 (q) , 65.0 (CH_2), 65.0 (CH_2), 60.7 (CH_2), 56.7 (CH), 34.7 (CH_2), 31.3 (CH_2), 26.8 (CH_3), 24.1 (CH_3), 19.4 (q), 12.5

(CH_2), 7.1 (CH_3), 6.4 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2957, 1715, 1629, 1428, 1114; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{55}N_2O_5Si_2$ $[M+NH_4]^+$, 651.3644, found 651.3644.

Minor diastereomer 252: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 4H, Ar**H**), 7.51 – 7.35 (m, 6H, Ar**H**), 6.49 (t, J = 1.8 Hz, 1H, C=C**H**), 4.54 (dd, $J_{AB, AX}$ = 18.8, 1.8 Hz, 1H, CH_2O), 4.43 (dd, $J_{BA, BX}$ = 18.8, 1.9 Hz, 1H, CH_2O), 3.92 – 3.64 (m, 4H, OCH_2CH_2O), 2.72 – 2.61 (m, 2H, 1 × CH_2CN, 1 × C**H**CH_2), 2.48 (dd, J = 17.9, 10.3 Hz, 1H, CH_2CN), 1.96 (td, J = 13.1, 4.8 Hz, 1H, CH_3CCH_2), 1.69 – 1.61 (m, 1H, CH_3CCH_2), 1.53 – 1.44 (m, 1H, $CH_3CCH_2CH_2$), 1.31 – 1.22 (m, 1H, $CH_3CCH_2CH_2$), 1.19 (s, 3H, CH_3CCH_2), 1.08 (s, 9H, SiC(CH_3)$_3$), 0.81 (t, J = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.55 – 0.40 (m, 6H, Si(C$H_2$$CH_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.4 (q), 180.2 (q), 135.6 (CH), 135.5 (CH), 132.6 (q), 132.5 (q), 130.3 (CH), 130.2 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 118.8 (q), 109.1 (q), 81.7 (q), 64.9 (CH_2), 64.8 (CH_2), 60.7 (CH_2), 51.6 (CH), 34.0 (CH_2), 32.2 (CH_2), 26.8 (CH_3), 24.0 (CH_3), 19.4 (q), 14.5 (CH_2), 7.2 (CH_3), 6.7 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2956, 1715, 1631, 1428, 1113; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{55}N_2O_5Si_2$ $[M+NH_4]^+$, 651.3644, found 651.3636.

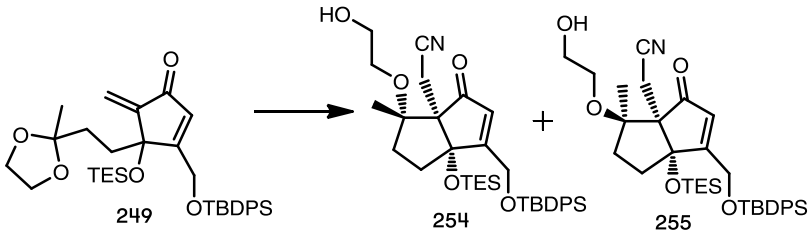
2-(2-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-5-oxo-2-(3-oxobutyl)cyclopent-3-enyl)acetonitrile **253**



Exo-methylene **205** (20 mg, 0.036 mmol, 1 equiv) was dissolved in anhydrous DCM (3 mL) and cooled to 0 °C before the dropwise addition of diethylaluminium cyanide (78.2 µL, 1M solution in toluene, 0.078 mmol, 2.2 equiv). The reaction mixture was stirred at 0 °C for 4 hr before quenching with excess saturated NH_4Cl solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished a single diastereomer of the title compound **253** as a colourless oil (11.9 mg, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar**H**), 7.49 – 7.35 (m, 6H, Ar**H**), 6.49 (t, *J* = 1.7 Hz, 1H, C=C**H**CO), 4.62 (dd, *J* = 18.7, 1.6 Hz, 1H, C**H**$_2$OSi), 4.37 (dd, *J* = 18.8, 1.8 Hz, 1H, C**H**$_2$OSi), 3.14 – 3.07 (m, 1H, C**H**$_2$), 2.95 (t, *J* = 6.9 Hz, 1H, CH$_2$C**H**), 2.73 (dd, *J* = 17.4, 6.3 Hz, 1H, C**H**$_2$), 2.39 (dd, *J* = 17.4, 7.6 Hz, 1H, C**H**$_2$), 2.03 (s, 3H, C**H**$_3$CO), 2.00 – 1.88 (m, 1H, C**H**$_2$), 1.42 (t, *J* = 7.3 Hz, 2H, C**H**$_2$CN), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 0.73 (s, 9H, SiC(C**H**$_3$)$_3$), 0.07 (s, 3H, SiC**H**$_3$), 0.02 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.4 (q), 199.5 (q), 180.8 (q), 135.5 (CH), 135.4 (CH), 132.5 (q), 132.4 (q), 130.2 (CH), 128.0 (CH), 128.0 (CH), 126.8 (CH), 117.8 (q), 82.2 (q) , 60.8 (CH_2), 56.6 (CH), 38.5 (CH_2), 30.6 (CH_2), 30.1 (CH_3), 26.8 (CH_3), 25.5 (CH_3), 19.3 (q), 18.1 (q), 12.7 (CH_2), -2.2 (CH_3), -2.9 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2930, 2857, 2359, 1715, 1708, 1471, 1112; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{48}NO_4Si_2$ $[M+H]^+$, 590.3116, found 590.3117.

2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(2-hydroxyethoxy)-3-methyl-4-oxo-6a-(triethylsilyloxy)-1,2,3,3a,4,6a-hexahydropentalen-3a-yl)acetonitrile **254** and **255**

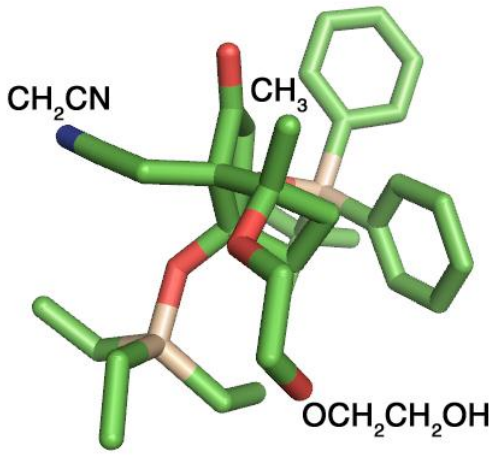


Exo-methylene **249** (1 g, 1.65 mmol, 1 equiv) was dissolved in anhydrous toluene (40 mL mL) under N_2, cooled to 0 °C and left to stir for 10 mins before dropwise addition of diethylaluminium cyanide (1.9 mL, 1 M in toluene, 1.9 mmol, 1.15 equiv). The reaction mixture was left stirring for 30 mins until the dropwise addition of $TiCl_4$ (4.94 mL, 1M solution in DCM, 4.94 mmol, 3 equiv) and the resultant mixture was left stirring for a further 30 mins before quenching with saturated $NaHCO_3$ solution (10mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 6:4) furnished a separable 15:1 diastereomeric mixture of **254** (751 mg, 72% yield) as a white solid and **255** (48.9, 5% yield) as an oil.

Major diastereomer 254: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 4H, Ar**H**), 7.49 – 7.35 (m, 6H, Ar**H**), 6.42 (t, J = 1.7 Hz, 1H, C=C**H**), 4.59 (dd, $J_{AB,\ AX}$ = 18.4, 1.9 Hz, 1H, C**H**$_2$O), 4.40 (dd, $J_{BA,\ BX}$ = 18.4, 1.7 Hz, 1H, C**H**$_2$O), 3.70 (s, 2H, OCH$_2$C**H**$_2$OH), 3.53 – 3.46 (m, 1H, OC**H**$_2$CH$_2$OH), 3.35 – 3.29 (m, 1H, OC**H**$_2$CH$_2$OH), 2.59 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 2.48 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 1.98 (s, 1H, O**H**), 1.95 – 1.84 (m, 2H, CH$_3$CC**H**$_2$C**H**$_2$), 1.73 – 1.64 (m, 1H, C**H**$_2$), 1.28 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 1.02 – 0.93 (m, 1H, C**H**$_2$), 0.81 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.57 – 0.39 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.2 (q), 180.2 (q), 135.5 (CH), 132.9 (q), 132.4 (q), 130.2 (CH), 130.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 119.1 (q), 89.4 (q), 83.0 (q), 65.2 (q), 62.8 (CH$_2$), 62.1 (CH$_2$), 61.3 (CH$_2$), 34.0 (CH$_2$), 32.2 (CH$_2$), 26.9 (CH$_3$), 19.4 (q),

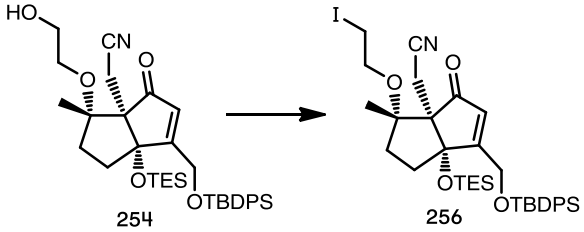
18.5 (CH_3), 17.0 (CH_2), 7.1 (CH_3), 6.6 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3461, 2955, 2251, 1709, 1634, 1112; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{55}N_2O_5Si_2$ $[M+NH_4]^+$ 651.3644, found 651.3650; **MP** 81-83 °C.

X-ray crystal structure for **254**:



Minor diastereomer 255: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 4H, Ar**H**), 7.50 – 7.34 (m, 6H, Ar**H**), 6.39 (t, *J* = 1.6 Hz, 1H, C=C**H**), 4.55 (dd, $J_{AB,\,AX}$ = 18.2, 1.8 Hz, 1H, C**H**$_2$O), 4.40 (dd, $J_{BA,\,BX}$ = 18.2, 1.7 Hz, 1H, C**H**$_2$O), 3.71 – 3.56 (m, 2H, OCH$_2$C**H**$_2$OH), 3.56 – 3.47 (m, 1H, OC**H**$_2$CH$_2$OH), 3.39 – 3.30 (m, 1H, OC**H**$_2$CH$_2$OH), 2.59 (d, *J* = 16.2 Hz, 1H, C**H**$_2$CN), 2.47 (d, *J* = 16.2 Hz, 1H, C**H**$_2$CN), 2.15 (s, 1H, O**H**), 1.99 – 1.83 (m, 2H, CH$_3$CC**H**$_2$CH$_2$), 1.81 – 1.67 (m, 2H, CH$_3$CC**H**$_2$CH$_2$), 1.35 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 0.81 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.58 – 0.39 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.2 (q), 178.7 (q), 135.6 (CH), 135.6 (CH), 132.9 (q), 132.5 (q), 130.2 (CH), 130.2 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 118.2 (q), 89.5 (q), 83.7 (q), 65.4 (q), 63.5 (CH_2), 62.0 (CH_2), 61.1 (CH_2), 35.6 (CH_2), 34.9 (CH_2), 26.9 (CH_3), 19.4 (q), 18.8 (CH_3), 18.5 (CH_2), 7.2 (CH_3), 6.6 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3451, 2958, 2251, 1709, 1634, 1113; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{55}N_2O_5Si_2$ $[M+NH_4]^+$ 651.3644, found 651.3635.

2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-(2-iodoethoxy)-3-methyl-4-oxo-6a-(triethylsilyloxy)-1,2,3,3a,4,6a-hexahydropentalen-3a-yl)acetonitrile **256**

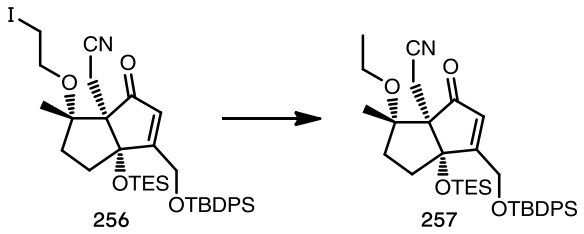


A solution of the bicycle **254** (600 mg, 0.95 mmol, 1 equiv), imidazole (161 mg, 2.37 mmol, 2.5 equiv) and PPh_3 (621 mg, 2.37 mmol, 2.5 equiv) in anhydrous DCM (15 mL) was stirred for 5 mins before addition in one portion of I_2 (480 mg, 1.89 mmol, 2 equiv). The resultant mixture was stirred for a further 1 hr before being quenched with excess NaS_2O_3 solution. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 17:3) gave the title compound **256** as an off-white solid (660 mg, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4H, Ar**H**), 7.49 – 7.34 (m, 6H, Ar**H**), 6.43 (t, J = 1.7 Hz, 1H, C=C**H**), 4.61 (dd, $J_{AB, AX}$ = 18.4, 1.9 Hz, 1H, C**H**$_2$O), 4.40 (dd, $J_{BA, BX}$ = 18.4, 1.7 Hz, 1H, C**H**$_2$O), 3.62 (dt, $J_{AB, AX}$ = 10.2, 6.9 Hz, 1H, OCH$_2$C**H**$_2$I), 3.48 (dt, $J_{BA, BX}$ = 10.2, 6.2 Hz, 1H, OCH$_2$C**H**$_2$I), 3.21 – 3.13 (m, 2H, OC**H**$_2$CH$_2$I), 2.66 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 2.55 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 1.94 (td, J = 12.9, 6.2 Hz, 1H, C**H**$_2$), 1.85 (dd, J = 14.0, 6.1 Hz, 1H, C**H**$_2$), 1.68 (dd, J = 12.4, 6.0 Hz, 1H, C**H**$_2$), 1.28 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 0.97 (td, J = 13.7, 6.2 Hz, 1H, C**H**$_2$), 0.81 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.58 – 0.38 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.1 (q), 180.4 (q), 135.6 (CH), 135.5 (CH), 133.0 (q), 132.4 (q), 130.2 (CH), 130.1 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 118.3 (q), 89.2 (q), 83.5 (q), 65.4 (q), 62.6 (CH_2), 61.4 (CH_2), 34.1(CH_2), 32.5 (CH_2), 26.9 (CH_3), 19.4 (q), 18.2 (CH_3), 17.0 (CH_2), 7.1 (CH_3), 6.6 (CH_2), 3.5 (CH_2); **IR** (thin film,

NaCl plate, cm^{-1}) 2956, 2251, 1709, 1634, 1462, 1111; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{54}IN_2O_4Si_2$ $[M+NH_4]^+$ 761.2661, found 761.2653; **MP** 108-110 °C.

2-(6-((*tert*-Butyldiphenylsilyloxy)methyl)-3-ethoxy-3-methyl-4-oxo-6a-(triethylsilyloxy)-1,2,3,3a,4,6a-hexahydropentalen-3a-yl)acetonitrile **257**

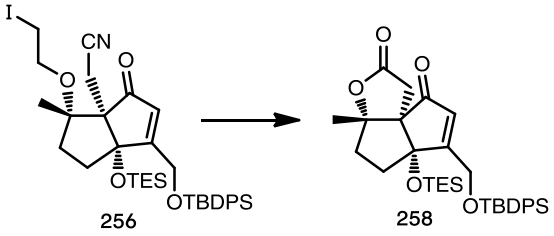


Bicycle **256** (40 mg, 0.054 mmol, 1 equiv) and activated Zn dust[100] (35.2 mg, 53.7 mmol, 10 equiv) were dissolved in dry MeOH (2 mL) and the resulting suspension was heated to 50 °C for 17 hr. The reaction mixture was filtered to remove the zinc and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane/EtOAc 9:1) to afford reduced **257** as a white solid (14.6 mg, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar**H**), 7.49 – 7.34 (m, 6H, Ar**H**), 6.42 (t, J = 1.7 Hz, 1H, C=C**H**), 4.62 (dd, $J_{AB, AX}$ = 18.4, 1.9 Hz, 1H, C**H**$_2$O), 4.40 (dd, $J_{BA, BX}$ = 18.4, 1.7 Hz, 1H, C**H**$_2$O), 3.37 (dt, $J_{AB, AX}$ = 14.0, 7.0 Hz, 1H, OC**H**$_2$CH$_3$), 3.27 – 3.18 (m, 1H, OC**H**$_2$CH$_3$), 2.63 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 2.55 (d, J = 16.5 Hz, 1H, C**H**$_2$CN), 1.94 – 1.81 (m, 2H, CH$_3$CC**H**$_2$C**H**$_2$), 1.64 (dd, J = 11.8, 6.0 Hz, 1H, C**H**$_2$), 1.24 (s, 3H, C**H**$_3$CCH$_2$), 1.12 (t, J = 7.0 Hz, 3H, OCH$_2$C**H**$_3$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$), 0.95 – 0.87 (m, 1H, C**H**$_2$), 0.85 – 0.76 (m, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.59 – 0.38 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.6 (q), 180.5 (q), 135.6 (CH), 135.5 (CH), 133.1 (q), 132.5 (q), 130.1 (CH), 130.1 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 118.5 (q), 89.3 (q), 82.4 (q), 65.5 (q), 61.5 (CH_2), 56.4 (CH_2), 34.2 (CH_2), 32.0 (CH_2), 26.9 (CH_3), 19.4 (q), 17.9 (CH_3), 16.8 (CH_2), 15.8 (CH_3), 7.1 (CH_3), 6.6 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2957, 2251, 1709, 1635, 1428,

1112; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{55}N_2O_4Si_2$ $[M+NH_4]^+$ 635.3695, found 635.3688; **MP** 108-110 °C.

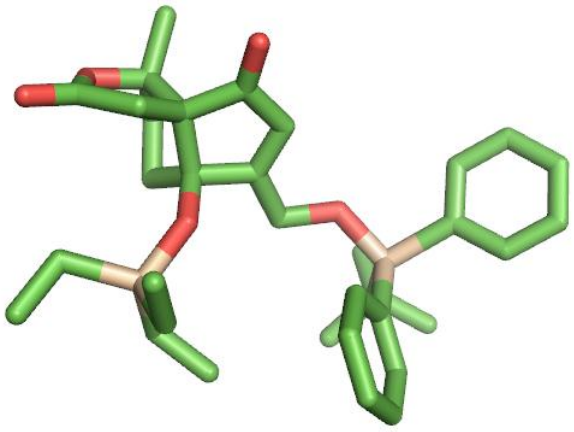
6-((*tert*-Butyldiphenylsilyloxy)methyl)-3a-methyl-5a-(triethylsilyloxy)-3a,4,5,5a-tetrahydro-1H-pentaleno[1-b]furan-2,8-dione **258**



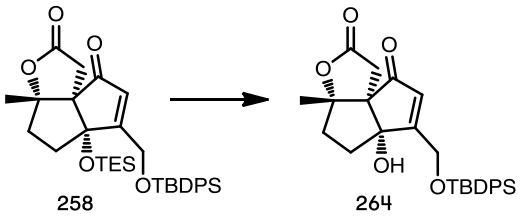
A solution of bicycle **256** (1200 mg, 1.61 mmol, 1 equiv) and activated Zn dust[100] (1055 mg, 16.1 mmol, 10 equiv) were dissolved in a solvent mixture of THF:0.1 M AcOH (37 mL, 9:1) and heated to reflux for 20 hr. The resultant suspension was filtered to remove the zinc, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished tricycle **258** as an off-white solid (846 mg, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar**H**), 7.50 – 7.36 (m, 6H, Ar**H**), 6.47 (t, J = 1.6 Hz, 1H, C=C**H**), 4.56 (dd, $J_{AB, AX}$ = 18.3, 1.8 Hz, 1H, C**H**$_2$O), 4.44 (dd, $J_{BA, BX}$ = 18.3, 1.7 Hz, 1H, C**H**$_2$O), 3.08 (d, J = 18.4 Hz, 1H, CC**H**$_2$CO), 2.69 (d, J = 18.4 Hz, 1H, CC**H**$_2$CO), 2.06 – 1.98 (m, 1H, C**H**$_2$), 1.94 – 1.82 (m, 2H, C**H**$_2$), 1.30 – 1.19 (m, 4H, C**H**$_3$CCH$_2$, C**H**$_2$), 1.10 (s, 9H, SiC(C**H**$_3$)$_3$), 0.80 (t, J = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.53 – 0.35 (m, 6H, Si(C**H**$_2$CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.0 (q), 178.7 (q), 174.9 (q), 135.5 (CH), 135.4 (CH), 132.6 (q), 132.3 (q), 130.2 (CH), 129.2 (CH), 128.0 (CH), 128.0 (CH), 92.5 (q), 88.8 (q), 66.6 (q), 60.7 (CH_2), 34.4 (CH_2), 32.8 (CH_2), 31.9 (CH_2), 26.8 (CH_3), 22.8 (CH_3), 19.3 (q), 6.9 (CH_3), 6.4 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2958, 1781, 1715, 1630, 1428, 1112; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{50}NO_5Si_2$ $[M+NH_4]^+$ 608.3222, found 608.3214; **MP** 76–78 °C.

X-ray crystal structure for **258**:



6-((*tert*-Butyldiphenylsilyloxy)methyl)-5a-hydroxy-3a-methyl-3a,4,5,5a-tetrahydro-1H-pentaleno[1-b]furan-2,8-dione **264**

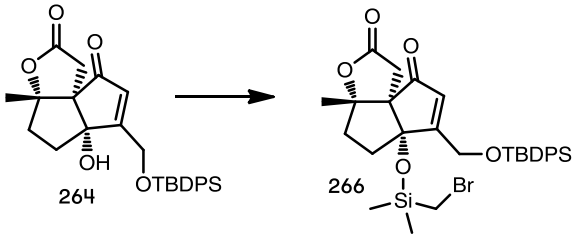


A solution of tricycle **258** (120 mg, 0.20 mmol, 1 equiv) was dissolved in a solvent mixture of THF:0.05 M HCl (40 mL, 79:1) and heated to reflux for 7 hr. The reaction mixture was diluted with brine and extracted twice with EtOAc. The organic extracts were dried over $MgSO_4$, filtered and solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 7:3) furnished tertiary alcohol **264** as an off-white solid (68.3 mg, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.59 (m, 4H, Ar**H**), 7.52 – 7.35 (m, 6H, Ar**H**), 6.30 (t, J = 1.6 Hz, 1H, C=C**H**), 4.70 (dd, $J_{AB, AX}$ = 17.6, 1.8 Hz, 1H, C**H**$_2$O), 4.61 (dd, $J_{BA, BX}$ = 17.6, 1.5 Hz, 1H, C**H**$_2$O), 3.04 (d, J = 18.2 Hz, 1H, CC**H**$_2$CO), 2.87 (s, 1H, O**H**), 2.79 (d, J = 18.2 Hz, 1H, CC**H**$_2$CO), 2.11 – 2.02 (m, 2H, CH_3CC**H**$_2$,

$CH_3CCH_2CH_2$), 1.96 (td, J = 13.6, 6.9 Hz, 1H, CH_2), 1.57 (s, 1H), 1.32 – 1.20 (m, 4H, CH_3CCH_2, CH_2), 1.09 (s, 9H, $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.0 (q), 177.0 (q), 175.1 (q), 135.7 (CH), 135.6 (CH), 132.2 (q), 132.1 (q), 130.5 (CH), 130.4 (CH), 130.1 (CH), 128.2 (CH), 128.2 (CH), 93.6 (q), 87.5 (q), 65.6 (q), 61.1 (CH_2), 34.5 (CH_2), 33.0 (CH_2), 31.8 (CH_2), 26.9 (CH_3), 22.7 (CH_3), 19.3 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3411, 2932, 1757, 1713, 1626, 1112; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{36}NO_5Si$ $[M+NH_4]^+$ 494.2357, found 494.2349; **MP** 110-112 °C.

5a-((Bromomethyl)dimethylsilyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-3a-methyl-3a,4,5,5a-tetrahydro-1H-pentaleno[1-b]furan-2,8-dione **266**

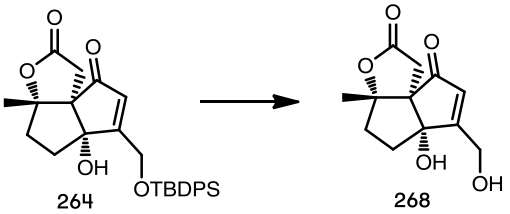


A solution of tricycle **264** (100 mg, 0.21 mmol, 1 equiv), imidazole (118 mg, 0.63 mmol, 3 equiv), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv) in anhydrous DCM (6 mL) were stirred at RT before adding (bromomethyl)chlorodimethylsilane (85 µL, 0.63 mmol, 3 equiv). The resultant mixture was heated to reflux for 3 hr before quenching with brine and extracted with DCM. The organic extracts were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 17:3) afforded the title compound **266** as a white solid (125 mg, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar**H**), 7.50 – 7.45 (m, 2H, Ar**H**), 7.44 – 7.38 (m, 4H, Ar**H**), 4.59 (dd, $J_{AB,\,AX}$ = 18.4, 1.9 Hz, 1H, CH_2O), 4.47 (dd, $J_{BA,\,BX}$ = 18.4, 1.9 Hz, 1H, CH_2O), 3.10 (d, J = 18.4 Hz, 1H, CCH_2CO), 2.65 (d, J = 18.4 Hz, 1H, CCH_2CO), 2.23 (s, 2H, CH_2Br), 2.04 (dd, J = 14.2, 6.1 Hz, 1H, CH_2), 2.00 – 1.87 (m, 2H, CH_2), 1.32 – 1.19 (m, 4H, CH_3CCH_2, CH_2), 1.10 (s, 9H, $SiC(CH_3)_3$),

0.17 (s, 3H, SiC**H**$_3$), 0.13 (s, 3H, SiC**H**$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.5 (q), 178.0 (q), 174.7 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.3 (q), 130.4 (CH), 130.4 (CH), 129.7 (CH), 128.2 (CH), 128.2 (CH), 92.6 (q), 89.4 (q), 66.5 (q), 60.7 (CH_2), 34.5 (CH_2), 32.6 (CH_2), 32.2 (CH_2), 26.9 (CH_3), 22.7 (CH_3), 19.4 (q), 16.2 (CH_2), -0.5 (CH_3), -0.5 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2932, 2360, 1774, 1714, 1630, 1110; **HRMS** (ESI) *m/z* calcd for $C_{31}H_{43}BrNO_5Si_2$ $[M+NH_4]^+$ 644.1858, found 644.1858; **MP** 101-103 °C.

5a-Hydroxy-6-(hydroxymethyl)-3a-methyl-3a,4,5,5a-tetrahydro-1H-pentaleno[1-b]furan-2,8-dione **268**

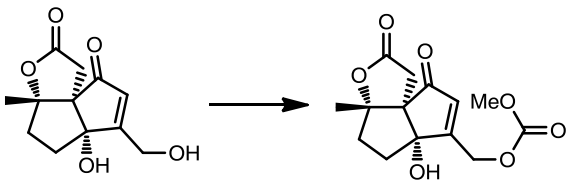


A solution of tertiary alcohol **264** (110 mg, 0.23 mmol, 1 equiv) dissolved in MeCN (6 mL) was stirred for 10 mins at 50 °C in a plastic container before the addition of HF (1.2 mL, 48% Aq HF). The resulting mixture was stirred for a further 3 hr before diluting with 1 M NaOH and ensuring the pH of the solution was neutralised. The EtOAc extracts of this mixture were washed with brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) furnished diol **268** as a white solid (846 mg, 89% yield).

^{1}H NMR (500 MHz, CD_3OD) δ 6.26 (t, *J* = 1.8 Hz, 1H, C=C**H**), 4.58 – 4.56 (m, 2H, C**H**$_2$OH), 3.02 (d, *J* = 18.1 Hz, 1H, CC**H**$_2$CO), 2.73 (d, *J* = 18.1 Hz, 1H, CC**H**$_2$CO), 2.21 (dd, *J* = 13.4, 6.3 Hz, 1H, C**H**$_2$), 2.08 (dd, *J* = 14.4, 6.7 Hz, 1H, C**H**$_2$), 1.88 (td, *J* = 13.7, 6.7 Hz, 1H, C**H**$_2$), 1.56 (td, *J* = 14.2, 6.4 Hz, 1H, C**H**$_2$), 1.27 (s, 3H, C**H**$_3$CCH$_2$); **^{13}C NMR** (126 MHz, CD_3OD) δ 203.9 (q), 182.8 (q), 177.1 (q), 129.4 (CH), 95.3 (q), 88.0 (q), 66.4 (q), 59.3 (q), 35.2 (CH_2), 33.1 (CH_2), 32.7 (CH_2), 22.8

(CH_3); **IR** (KBr disc, cm^{-1}) 3400, 2917, 2521, 1760, 1710, 1627, 1095; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{18}NO_5$ $[M+NH_4]^+$ 256.1179, found 256.1183; **MP** 130-132 °C.

(5a-Hydroxy-3a-methyl-2,8-dioxo-2,3a,4,5,5a,8-hexahydro-1H-pentaleno[1-b]furan-6-yl)methyl methyl carbonate **269**

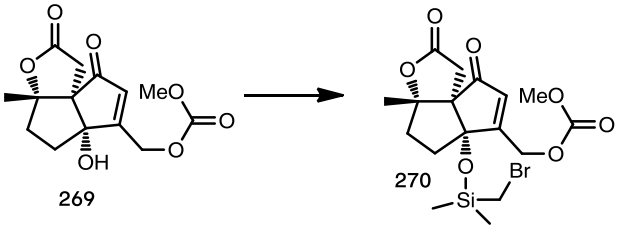


268 269

Diol **268** (47 mg, 0.20 mmol, 1 equiv), triethylamine (63.9 mg, 0.63 mmol, 3.2 equiv), DMAP (5 mg, 0.04 mmol, 0.2 equiv) and methyl chloroformate (28 mg, 0.30 mmol, 1.5 equiv) were dissolved in anhydrous THF (6 mL) and heated to reflux for 16 hr. The reaction mixture was diluted with brine and extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 1:1) furnished carbonate **269** as an oil (48 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (t, J = 1.5 Hz, 1H, C=C**H**), 5.12 (dd, $J_{AB, AX}$ = 17.0, 1.6 Hz, 1H, C**H**$_2$O), 5.07 (dd, $J_{BA, BX}$ = 17.0, 1.6 Hz, 1H, C**H**$_2$O), 3.84 (s, 3H, C**H**$_3$O), 3.75 (s, 1H, O**H**), 3.07 (d, J = 18.3 Hz, 1H, CC**H**$_2$CO), 2.82 (d, J = 18.3 Hz, 1H, CC**H**$_2$CO), 2.27 (dd, J = 13.3, 6.5 Hz, 1H, C**H**$_2$), 2.21 – 2.06 (m, 2H, CH_3CC**H**$_2$C**H**$_2$), 1.50 (td, J = 13.6, 6.6 Hz, 1H, C**H**$_2$), 1.29 (s, 3H, C**H**$_3$$CCH_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.6 (q), 175.6 (q), 172.2 (q), 155.6 (q), 130.3 (CH), 94.2 (q), 87.8 (q), 65.2 (q), 63.4 (CH_2), 55.7 (CH_3), 34.3 (CH_2), 32.9 (CH_2), 32.2 (CH_2), 22.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3416, 2931, 1755, 1631, 1446, 1264; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{17}O_7$ $[M+H]^+$ 297.0969, found 297.0968.

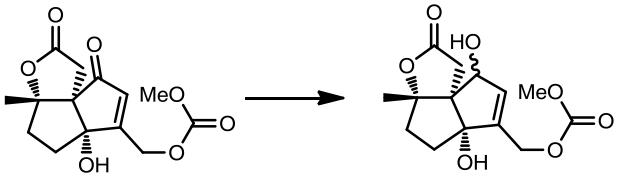
(5a-((Bromomethyl)dimethylsilyloxy)-3a-methyl-2,8-dioxo-2,3a,4,5,5a,8-hexahydro-1H-pentaleno[1-b]furan-6-yl)methyl methyl carbonate **270**



A solution of tertiary alcohol **269** (30 mg, 0.10 mmol, 1 equiv), imidazole (37 mg, 0.54 mmol, 5.3 equiv), DMAP (1.2 mg, 0.01 mmol, 0.1 equiv) in anhydrous DCM (4 mL) were stirred at RT before adding (bromomethyl)chlorodimethylsilane (34 µL, 0.25 mmol, 2.5 equiv). The resultant mixture was heated to reflux for 2 hr before quenching with brine and extracting with DCM. The organic extracts were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 7:3) afforded tricycle **270** as a colourless oil (37 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 – 6.24 (m, 1H, C=C**H**), 5.05 (d, J = 1.6 Hz, 2H, C**H$_2$**O), 3.85 (s, 3H, C**H$_3$**O), 3.13 (d, J = 18.4 Hz, 1H, CC**H$_2$**CO), 2.69 (d, J = 18.3 Hz, 1H, CC**H$_2$**CO), 2.46 (d, J = 1.3 Hz, 2H, C**H$_2$**Br), 2.32 (dd, J = 12.9, 6.2 Hz, 1H, C**H$_2$**), 2.21 (dd, J = 14.2, 6.7 Hz, 1H, C**H$_2$**), 2.12 (td, J = 13.2, 6.7 Hz, 1H, C**H$_2$**), 1.52 (td, J = 13.8, 6.3 Hz, 1H, C**H$_2$**), 1.28 (s, 3H, C**H$_3$**CCH$_2$), 0.38 (s, 3H, SiC**H$_3$**), 0.36 (s, 3H SiC**H$_3$**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.0 (q), 174.5 (q), 171.1 (q), 155.4 (q), 130.3 (CH), 92.7 (q), 90.0 (q), 66.2 (q), 63.3 (CH_2), 55.7 (CH_3), 34.6 (CH_2), 32.8, (CH_2), 32.3 (CH_2), 22.7 (CH_3), 16.3 (CH_2), -0.2 (CH_3), -0.2 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2961, 1755, 1633, 1446, 1260; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{24}BrO_7Si$ $[M+H]^+$ 447.0469, found 447.0473.

(5a,8-Dihydroxy-3a-methyl-2-oxo-2,3a,4,5,5a,8-hexahydro-1H-pentaleno[1-b]furan-6-yl)methyl methyl carbonate **275**

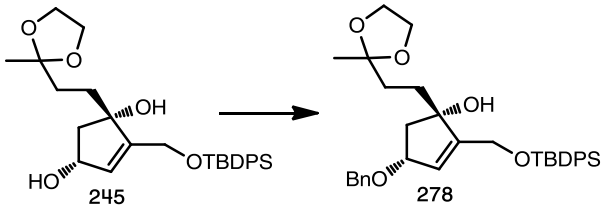


269 275

A solution of carbonate **269** (28 mg, 0.095 mmol, 1 equiv), $CeCl_3 \cdot 7H_2O$ (106 mg, 0.28 mmol, 3 equiv) in anhydrous MeOH (2.5 mL) was stirred and cooled to 0 °C before addition $NaBH_4$ (10.7 mg, 0.28 mmol, 3 equiv) in one portion. The resultant reaction mixture was stirred for 4 hr before being quenched with distilled H_2O (1 mL) and then diluted with EtOAc. The mixture was dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 2:8) furnished a single diastereomer of diol **275** as a colourless oil (18 mg, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.87 (m, 1H, C=C**H**), 4.82 – 4.78 (m, 1H, C**H**OH), 4.77 (s, 2H, C**H$_2$**O), 3.80 (s, 3H, C**H$_3$**O), 3.02 (s, 1H, CO**H**), 2.88 (d, *J* = 17.6 Hz, 1H, CC**H$_2$**CO), 2.70 (d, *J* = 17.6 Hz, 1H, CC**H$_2$**CO), 2.27 – 2.10 (m, 3H, C**H$_2$**, CHO**H**), 1.92 – 1.74 (m, 3H, C**H$_2$**, C**H$_2$**), 1.62 (s, 3H, C**H$_3$**CCH$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.1 (q), 155.9 (q), 143.2 (q), 132.9 (CH), 97.5 (q), 92.4 (q), 78.6 (CH), 63.3 (CH_2), 62.8 (q), 55.3 (CH_3), 37.2 (CH_2), 35.5 (CH_2), 34.9 (CH_2), 23.0 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3411, 2960, 1744, 1448, 1276; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{22}NO_7$ $[M+NH_4]^+$ 316.1391, found 316.1392.

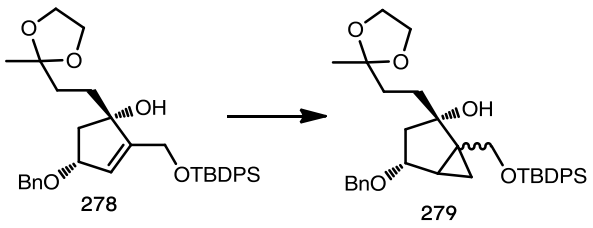
4-(Benzyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol **278**



A solution of diol **245** (100 mg, 0.21 mmol, 1 equiv) and TBAI (38 mg, 0.10 mmol, 0.5 equiv) in anhydrous THF (6 mL) was stirred at RT before adding NaH (15 mg, 60% mineral oil, 0.62 mmol, 3 equiv) followed by dropwise addition of BnBr (37 µL, 0.41 mmol, 1.5 equiv). The reaction was stirred for 6 hr and the reaction was quenched with distilled H_2O (2 mL), dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography (SiO_2, hexane/EtOAc 1:1) furnished alcohol **278** as a brown oil (75 mg, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.63 (m, 4H, Ar**H**), 7.48 – 7.27 (m, 11H, Ar**H**), 5.95 (s, 1H, C=C**H**),), 4.57 (d, J = 11.7 Hz, 1H, C**H$_2$**O), 4.53 (d, J = 11.7 Hz, 1H, C**H$_2$**O), 4.46 – 4.26 (m, 3H, C**H$_2$**Ph, C**H**OH), 3.97 – 3.76 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.56 (d, J = 2.1 Hz, 1H, O**H**), 2.42 (dd, $J_{AB,\ AX}$ = 14.0, 6.8 Hz, 1H, C**H$_2$**CH), 1.96 (dd, $J_{BA,\ BX}$ = 14.0, 3.5 Hz, 1H, C**H$_2$**CH), 1.80 (d, J = 4.5 Hz, 1H, C**H$_2$**), 1.66 (dd, J = 13.0, 3.5 Hz, 1H, C**H$_2$**), 1.48 (dt, J = 13.5, 6.7 Hz, 2H, C**H$_2$**), 1.25 (s, 3H, C**H$_3$**CCH$_2$), 1.07 (s, 9H, SiC(C**H$_3$**)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.8 (q), 138.7 (q), 135.8 (CH), 135.7 (CH), 133.1 (q), 133.1 (q), 130.0 (CH), 129.9 (CH), 128.6 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 109.9 (q), 83.4 (q), 80.0 (CH), 70.9 (CH_2), 64.8 (CH_2), 60.8 (CH_2), 45.7 (CH_2), 33.9 (CH_2), 32.7 (CH_2), 26.9 (CH_3), 24.0 (CH_3), 19.3 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3445, 2931, 2359, 1739, 1428, 1113; **HRMS** (ESI) *m/z* calcd for $C_{35}H_{48}NO_5Si$ $[M+NH_4]^+$ 590.3296, found 590.3301.

4-(Benzyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)bicyclo[3.1.0]hexan-2-ol **279**



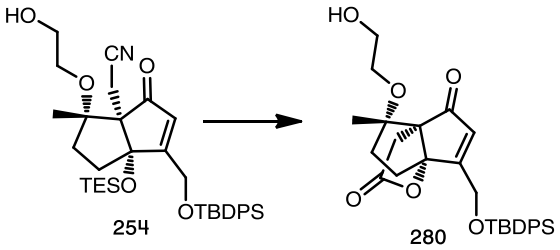
Method A: A solution of alcohol **278** (50 mg, 0.09 mmol, 1 equiv), Zn-Cu[129,143] (46 mg, 0.70 mmol, 8 equiv), CH_2I_2 (28 µL, 0.35 mmol, 4 equiv) in anhydrous Et_2O (5 mL) was stirred for 5 mins before I_2 (5.5 mg, 0.04 mmol, 0.5 equiv) was added in one portion. The reaction mixture was heated to reflux and left stirring for 17 hr before the reaction was quenched with distilled H_2O (2 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 7:3) furnished bicycle **279** as a yellow oil (13.8 mg, 25% yield).

Method B: A solution of alcohol **278** (80 mg, 0.14 mmol, 1 equiv) and Et_2Zn (138 µL, 1 M solution in toluene, 1.11 mmol, 8 equiv) in anhydrous Et_2O (5 mL) was cooled to 0 °C and was stirred for 5 mins before CH_2I_2 (181 µL, 2.23 mmol, 16 equiv)was added in one portion. The reaction mixture was left stirring for 24 hr at RT before brine and DCM was added, the organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 7:3) furnished bicycle **279** as a yellow oil (15 mg, 18% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.59 (m, 4H, Ar**H**), 7.50 – 7.27 (m, 11H, Ar**H**), 4.51 (d, J = 11.7 Hz, 1H, C**H**$_2$Ph), 4.44 (d, J = 11.7 Hz, 1H, C**H**$_2$Ph), 4.24 (dd, $J_{AB, AX}$ = 10.6, 1.0 Hz, 1H, C**H**$_2$OSi), 4.08 – 4.00 (m, 1H, C**H**OH), 4.00 – 3.85 (m, 4H, OC**H**$_2$C**H**$_2$O), 3.16 (d, J = 10.6 Hz, 1H, C**H**$_2$OSi), 2.66 (s, 1H, O**H**), 2.15 – 1.99 (m, 2H, C**H**$_2$, CC**H**$_2$CH), 1.94 – 1.81 (m, 1H, C**H**$_2$), 1.74 – 1.60 (m, 2H, CH_3CC**H**$_2$C**H**$_2$),

1.51 – 1.38 (m, 2H, CCH_2CH, CCH_2CH), 1.34 (s, 3H, CH_3CCH_2), 1.06 (s, 9H, $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7 (q), 135.8 (CH), 135.7 (CH), 133.1 (q), 133.0 (q), 130.0 (CH), 130.0 (CH), 128.5 (CH), 127.9 (CH), 127.9 (CH), 127.9 (CH), 127.7 (CH), 110.2 (q), 79.3 (CH), 71.3 (CH_2), 66.4 (CH_2), 64.8 (CH_2), 64.8 (CH_2), 38.3 (CH_2), 36.4(q), 33.5 (CH_2), 33.0 (CH_2), 27.0 (CH_3), 24.6 (CH_3), 24.1 (CH), 19.2 (q), 11.3 (CH_2);); **IR** (thin film, NaCl plate, cm^{-1}) 3564, 2930, , 2359, 1428, 1066; **HRMS** (ESI) *m/z* calcd for $C_{36}H_{46}NaO_5Si$ $[M+Na]^+$ 609.3007, found 609.3008.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-(2-hydroxyethoxy)-11-methyl-2-oxatricyclo[3.3.3.0^{1,5}]undec-7-ene-3,6-dione **280**

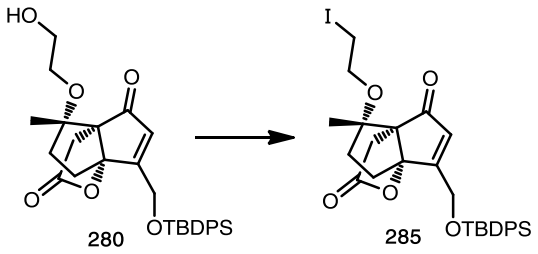


Method A: A solution of bicycle **254** (50 mg, 0.08 mmol, 1 equiv) was dissolved in anhydrous DCM (80 mL) and stirred at RT before the dropwise addition of $BF_3{\cdot}Et_2O$ (161 µL, 1.26 mmol, 16 equiv). The reaction mixture was then heated to precisely 30 °C and stirred for 9 hr at which time the reaction was diluted with brine and extracted twice with DCM. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 1:1) furnished tricyclic alcohol **280** (27.9 mg, 68% yield) as an oil.

Tricyclic alcohol 280: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.58 (m, 4H, Ar**H**), 7.51 – 7.34 (m, 6H, Ar**H**), 6.29 (t, J = 1.9 Hz, 1H, C=C**H**), 4.70 (dd, $J_{AB,\,AX}$ = 19.1, 1.9 Hz, 1H, CH_2O), 4.52 (dd, $J_{BA,\,BX}$ = 19.1, 1.9 Hz, 1H, CH_2O), 3.82 – 3.67 (m, 2H, OCH_2CH_2OH), 3.55 – 3.41 (m, 2H, OCH_2CH_2OH), 3.21 (d, J = 18.7 Hz, 1H,

CC**H**$_2$CO), 2.41 – 2.26 (m, 2H, CC**H**$_2$CO, O**H**), 2.13 (dt, J = 13.6, 6.9 Hz, 1H, CH_3CC**H**$_2$), 2.01 (dt, J = 14.4, 7.3 Hz, 1H, CH_3CCH_2C**H**$_2$), 1.71 (dt, J = 13.8, 6.7 Hz, 1H, CH_3CCH_2C**H**$_2$), 1.52 (dt, J = 14.0, 7.1 Hz, 1H, CH_3CC**H**$_2$), 1.29 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.9 (q), 176.0 (q), 175.5 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.4 (q), 130.4 (CH), 130.3 (CH), 129.5 (CH), 128.2 (CH), 128.1 (CH), 97.9 (q), 82.5 (q), 66.4 (q), 63.7 (CH_2), 62.3 (CH_2), 60.6 (CH_2), 36.9 (CH_2), 33.1 (CH_2), 31.4 (CH_2), 26.9 (CH_3), 19.3 (q), 18.0 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3457, 3072, 2930, 1789, 1712, 1627, 1114; **HRMS** (ESI) *m/z* calcd for $C_{30}H_{40}NO_6Si$ $[M+NH_4]^+$ 538.2619, found 538.2615.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-(2-iodoethoxy)-11-methyl-2-oxatricyclo[3.3.3.0^{1,5}]undec-7-ene-3,6-dione **285**

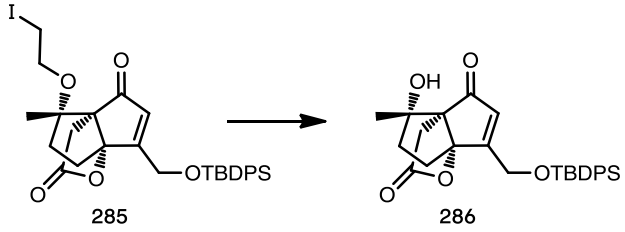


A solution of tricycle **280** (110 mg, 0.22 mmol, 1 equiv), imidazole (38 mg, 0.55 mmol, 2.5 equiv) and PPh_3 (145 mg, 0.55 mmol, 2.5 equiv) in dry DCM (6 mL) was stirred for 5 mins at RT before the addition of I_2 (112 mg, 0.44 mmol, 2 equiv) in one portion. The reaction mixture was stirred for 2 hr before being diluted with saturated $Na_2S_2O_3$ solution and extracted with EtOAc. The EtOAc extracts were washed with brine and dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 17:3) delivered the title compound **285** as white solid (95 mg, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 4H, Ar**H**), 7.50 – 7.35 (m, 6H, Ar**H**), 6.29 (t, J = 1.9 Hz, 1H, C=C**H**), 4.71 (dd, $J_{AB, AX}$ = 19.1, 2.0 Hz, 1H, C**H**$_2$O), 4.53 (dd,

$J_{BA, BX}$ = 19.1, 1.9 Hz, 1H, C**H**$_2$O), 3.66 (dt, J = 10.2, 6.2 Hz, 1H, ICH$_2$C**H**$_2$), 3.56 (dt, J = 10.2, 6.3 Hz, 1H, ICH$_2$C**H**$_2$), 3.29 (d, J = 18.7 Hz, 1H, C**H**$_2$CO), 3.24 – 3.16 (m, 2H, C**H**$_2$I), 2.33 (d, J = 18.7 Hz, 1H, C**H**$_2$CO), 2.14 – 2.02 (m, 2H, CH$_3$CC**H**$_2$, CH$_3$CCH$_2$C**H**$_2$), 1.78 – 1.68 (m, 1H, C**H**$_2$), 1.51 – 1.41 (m, 1H, C**H**$_2$), 1.30 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.1 (q), 176.2 (q), 174.9 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.4 (q), 130.4 (CH), 130.3 (CH), 129.6 (CH), 128.2 (CH), 128.1 (CH), 97.5 (q), 82.5 (q), 66.5 (q), 63.2 (CH$_2$), 60.7 (CH$_2$), 36.6 (CH$_2$), 32.9 (CH$_2$), 31.4 (CH$_2$), 26.9 (CH$_3$), 19.3 (q), 18.1 (CH$_3$), 3.2 (CH$_2$); **IR** (thin film, NaCl plate, cm^{-1}) 2955, 2854, 1778, 1714, 1625, 1428, 1101; **HRMS** (ESI) *m/z* calcd for $C_{30}H_{39}INO_5Si$ $[M+NH_4]^+$ 648.1637, found 648.1634; **MP** 128-130 °C.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-hydroxy-11-methyl-2-oxatricyclo[3.3.3.0^{1,5}]undec-7-ene-3,6-dione **286**



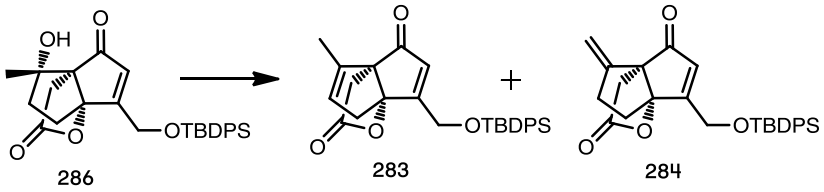
A solution of tricycle **285** (76 mg, 0.12 mmol, 1 equiv) and activated Zn dust[100] (79 mg, 1.2 mmol, 10 equiv) in a solvent mixture of THF:0.1M AcOH (3 mL, 9:1) was heated to reflux for 3 hr. The reaction mixture was diluted in brine and extracted twice with EtOAc. The EtOAc extracts were combined and dried over $MgSO_4$ and evaporated to dryness. Flash column chromatography (SiO_2, hexane/EtOAc 17:3) delivered the tertiary alcohol **286** as a white solid (37 mg, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 6.8, 1.2 Hz, 4H, Ar**H**), 7.50 – 7.35 (m, 6H, Ar**H**), 6.30 (t, J = 1.8 Hz, 1H, C=C**H**), 4.71 (dd, $J_{AB, AX}$ = 19.1, 1.9 Hz, 1H, C**H**$_2$O), 4.55 (dd, $J_{BA, BX}$ = 19.1, 1.8 Hz, 1H, C**H**$_2$O), 3.18 (d, J = 18.8 Hz, 1H, C**H**$_2$CO), 2.34

(d, *J* = 18.8 Hz, 1H, C**H**$_2$CO), 2.17 (ddd, *J* = 13.7, 10.1, 7.0 Hz, 1H, C**H**$_2$), 1.90 (ddd, *J* = 13.3, 6.9, 4.1 Hz, 1H, C**H**$_2$), 1.79 (ddd, *J* = 13.7, 6.7, 4.1 Hz, 1H, C**H**$_2$), 1.67 (s, 1H, O**H**), 1.54 (ddd, *J* = 13.4, 10.1, 6.8 Hz, 1H, C**H**$_2$), 1.39 (s, 3H, C**H**$_3$CCH$_2$), 1.09 (s, 9H, SiC(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.6 (q), 176.1 (q), 175.0 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.4 (q), 130.3 (CH), 130.3 (CH), 129.7 (CH), 128.1 (CH), 128.1 (CH), 97.6 (q), 77.9 (q), 66.0 (q), 60.7 (CH_2), 40.4 (CH_2), 32.9 (CH_2), 31.8 (CH_2), 26.9 (CH_3), 23.9 (CH_3), 19.3 (q); **IR** (thin film, NaCl plate, cm^{-1}) 3474, 3072, 2932, 2252, 1785, 1709, 1428, 1115; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{36}NO_5Si$ $[M+NH_4]^+$ 494.2357, found 494.2353.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-methyl-2-oxatricyclo[3.3.3.0^{1,5}]undeca-7,10-diene-3,6- dione **283** and

8-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-11- methylidene-2-oxatricyclo[3.3.3.0^{1,5}]undec-7- ene-3,6-dione **284**

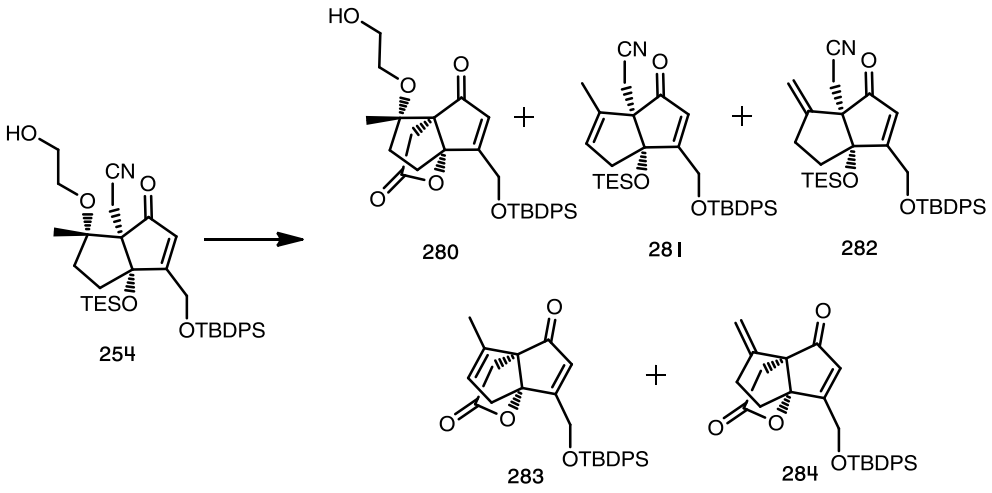


A solution of tertiary alcohol **286** (36 mg, 0.08 mmol, 1 equiv) and Burgess reagent (27 mg, 0.11 mmol, 1.5 equiv) was dissolved in anhydrous DCM (5 mL) and heated to reflux for 48 hr. The reaction mixture was quenched with distilled H_2O (1 mL) and dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished an inseparable mixture of regioisomers *endo*-**283**:*exo*-**284** (1:1.2) (26 mg, 76% combined yield) as a yellow solid.

***Endo*-283/*Exo*-284:** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 4H, Ar**H**), 7.55 – 7.32 (m, 6H, Ar**H**), 6.38 (t, *J* = 1.9 Hz, 1H, *exo* CH_2C=C**H**), 6.33 (t, *J* = 1.9 Hz, 1H,

endo $CH_2C=CH$), 5.30 – 5.22 (m, 1H, *exo* $CH_2=C$/*endo* $CH=CCH_3$), 5.13 (t, J = 1.8 Hz, 1H, *exo* $CH_2=C$), 4.78 – 4.68 (m, 2H, *endo/exo* CH_2O), 4.61 – 4.50 (m, 2H, *endo/exo* CH_2O), 2.92 – 2.61 (m, 3H, CH_2CO, *endo* CH_2), 2.59 – 2.48 (m, 2H, *endo* CH_2/*exo* CH_2), 2.34 – 2.23 (m, 1H, *exo* CH_2), 2.00 – 1.92 (m, 2H, *exo* CH_2), 1.87 – 1.78 (m, 3H, *endo* $CH_3C=CH$), 1.14 – 1.01 (m, 9H, *endo/exo* $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) endo/*exo* δ 202.1 (q), 201.8 (q), 175.5 (q), 175.0 (q), 174.6 (q), 174.3 (q), 147.5 (q), 137.3 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.4 (q), 132.4 (q), 130.3 (CH), 130.3 (CH), 130.3 (CH), 129.7 (CH), 129.2 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 124.6 (CH), 110.9 (CH_2), 98.1 (q), 96.7 (q), 68.2 (q), 63.2 (q), 60.8 (CH_2), 60.8 (CH_2), 40.8 (CH_2), 38.2 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 26.9 (CH_3), 19.3 (q), 13.4 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3068, 2359, 2253, 1785, 1709, 1628, 1428, 1106; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{34}NO_4Si$ $[M+NH_4]^+$ 476.2252, found 476.2246.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-(2-hydroxyethoxy)-11-methyl-2-oxatricyclo[3.3.3.0^{1,5}]undec-7-ene-3,6-dione **280**, 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-3-methyl-4-oxo-6a-(triethylsilyloxy)-1,3a,4,6a-tetrahydropentalen-3a-yl)acetonitrile **281**, 2-(6-((*tert*-butyldiphenylsilyloxy)methyl)-3-methylene-4-oxo-6a-(triethylsilyloxy)-1,2,3,3a,4,6a-hexahydropentalen-3a-yl)acetonitrile **282**, 8-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-11-methyl-2- oxatricyclo[3.3.3.0^{1,5}]undeca-7,10-diene-3,6- dione **283** and 8-{[(tert-butyldiphenylsilyl)oxy]methyl}-11-methylidene-2-oxatricyclo[3.3.3.0^{1,5}]undec-7- ene-3,6-dione **284**



Method B: A solution of bicycle **254** (515 mg, 0.81 mmol, 1 equiv) was dissolved in anhydrous DCM (80 mL) and stirred at RT before the dropwise addition of $BF_3{\cdot}Et_2O$ (1.43 mL, 10.57 mmol, 13 equiv). The reaction mixture was then heated to reflux and stirred for 6 hr at which time the reaction was diluted with brine and extracted twice with DCM. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 1:1) afforded a mixture of five products: **280** (56.6 mg, 13% yield) as an oil, an inseparable mixture of regioisomers *endo*-**281**:*exo*-**282** (1:1.5) as a brown oil (86.1 mg, 19%), an inseparable mixture of regioisomers *endo*-**283**:*exo*-**284**

(1:0.6) as a white solid (24.5 mg, 7%) and unreacted starting material **254** (36 mg, 7% yield).

Tricyclic alcohol 280: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.58 (m, 4H, Ar**H**), 7.51 – 7.34 (m, 6H, Ar**H**), 6.29 (t, J = 1.9 Hz, 1H, C=C**H**), 4.70 (dd, $J_{AB,\ AX}$ = 19.1, 1.9 Hz, 1H, C**H$_2$**O), 4.52 (dd, $J_{BA,\ BX}$ = 19.1, 1.9 Hz, 1H, C**H$_2$**O), 3.82 – 3.67 (m, 2H, OCH_2CH_2OH), 3.55 – 3.41 (m, 2H, OCH_2CH_2OH), 3.21 (d, J = 18.7 Hz, 1H, CCH_2CO), 2.41 – 2.26 (m, 2H, CCH_2CO, O**H**), 2.13 (dt, J = 13.6, 6.9 Hz, 1H, CH_3CCH_2), 2.01 (dt, J = 14.4, 7.3 Hz, 1H, $CH_3CCH_2CH_2$), 1.71 (dt, J = 13.8, 6.7 Hz, 1H, $CH_3CCH_2CH_2$), 1.52 (dt, J = 14.0, 7.1 Hz, 1H, CH_3CCH_2), 1.29 (s, 3H, CH_3CCH_2), 1.09 (s, 9H, $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.9 (q), 176.0 (q), 175.5 (q), 135.6 (CH), 135.6 (CH), 132.6 (q), 132.4 (q), 130.4 (CH), 130.3 (CH), 129.5 (CH), 128.2 (CH), 128.1 (CH), 97.9 (q), 82.5 (q), 66.4 (q), 63.7 (CH_2), 62.3 (CH_2), 60.6 (CH_2), 36.9 (CH_2), 33.1 (CH_2), 31.4 (CH_2), 26.9 (CH_3), 19.3 (q), 18.0 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3457, 3072, 2930, 1789, 1712, 1627, 1114; **HRMS** (ESI) *m/z* calcd for $C_{30}H_{40}NO_6Si$ $[M+NH_4]^+$ 538.2619, found 538.2615.

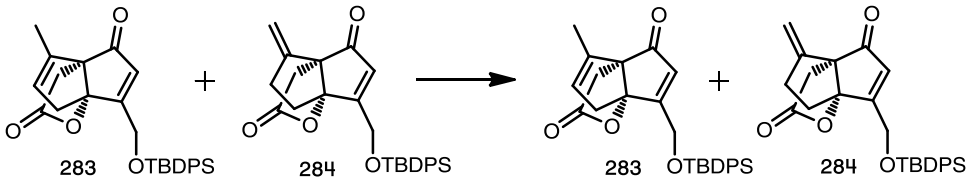
***Endo*-281/*Exo*-282** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 – 7.60 (m, 4H, Ar**H**), 7.51 – 7.35 (m, 6H, Ar**H**), 6.45 (t, J = 1.8 Hz, 1H, *exo* CH_2C=C**H**), 6.33 (t, J = 1.8 Hz, 1H, *endo* CH_2C=C**H**), 5.36 (d, J = 1.6 Hz, 1H, *endo* C**H**=CCH_3), 5.20 – 5.16 (m, 1H, *exo* C**H$_2$**=C), 5.15 – 5.10 (m, 1H, *exo* C**H$_2$**=C), 4.65 – 4.55 (m, 1H, *endo/exo* C**H$_2$**O), 4.50 – 4.38 (m, 2H, *endo/exo* C**H$_2$**O), 2.82 (d, J = 16.7 Hz, 1H, *exo* C**H$_2$**CN), 2.75 (d, J = 16.7 Hz, 1H, *endo* C**H$_2$**CN), 2.62 – 2.52 (m, 3H, *endo/exo* C**H$_2$**CN, C**H$_2$**), 2.52 – 2.37 (m, 2H, *endo/exo* C**H$_2$**), 2.05 – 1.87 (m, 3H, *endo/exo* C**H$_2$**, C**H$_2$**), 1.76 – 1.70 (m, 3H, *endo* C**H$_3$**C=CH), 1.09 (s, 9H, *endo/exo* $SiC(CH_3)_3$), 0.88 – 0.76 (m, 9H, *endo/exo* $Si(CH_2CH_3)_3$), 0.62 – 0.39 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.1 (q), 202.0 (q), 179.1 (q), 178.4 (q), 146.9 (q), 137.9 (q), 135.6 (CH), 135.6 (CH), 135.5 (CH), 135.3 (CH), 134.9 (CH), 134.6 (CH), 134.6 (CH), 132.8 (q), 132.8 (q), 132.7 (q), 132.7 (q), 132.5 (q), 132.5 (q), 130.4 (CH), 130.3 (CH), 130.3 (CH), 130.2 (CH), 130.2 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 128.1 (CH),

128.0 (CH), 125.8 (CH), 125.1 (CH), 118.1 (q), 117.7 (q), 111.7 (CH_2), 89.6 (q), 88.1 (q), 68.6 (q), 63.2 (q), 61.3 (CH_2), 60.7 (CH_2), 42.9 (CH_2), 34.6 (CH_2), 30.1 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 26.1 (CH_3), 19.7 (CH_2), 19.4 (q), 19.4 (q), 19.3 (q), 19.1 (q), 17.6 (CH_2), 13.4 (CH_3), 7.2 (CH_3), 7.1 (CH_3), 6.6 (CH_2), 6.5 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3072, 2957, 2359, 2253, 1716, 1630, 1590, 1428, 1114; **HRMS** (ESI) *m/z* calcd for $C_{34}H_{49}N_2O_3Si_2$ $[M+NH_4]^+$ 589.3276, found 589.3274.

Endo-283/Exo-284 **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 4H, Ar**H**), 7.51 – 7.32 (m, 6H, Ar**H**), 6.38 (t, *J* = 1.9 Hz, 1H, *exo* CH_2C=C**H**), 6.33 (t, *J* = 1.9 Hz, 1H, *endo* CH_2C=C**H**), 5.29 – 5.23 (m, 2H, *exo* C**H**$_2$=C/*endo* C**H**=CCH_3), 5.13 (t, *J* = 1.7 Hz, 1H, *exo* C**H**$_2$=C), 4.77 – 4.68 (m, 2H, *endo/exo* C**H**$_2$O), 4.60 – 4.51 (m, 2H, *endo/exo* C**H**$_2$O), 2.91 – 2.61 (m, 5H, *endo/exo* C**H**$_2$CO, *endo* C**H**$_2$), 2.34 – 2.22 (m, 2H, *endo/exo* C**H**$_2$), 2.01 – 1.93 (m, 1H, *exo* C**H**$_2$), 1.83 (d, *J* = 1.7 Hz, 3H, *endo* C**H**$_3$C=CH), 1.14 – 1.04 (m, 9H, *endo/exo* SiC(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.1 (q), 201.8 (q), 175.5 (q), 175.0 (q), 174.6 (q), 174.3 (q), 147.5 (q), 137.3 (q), 135.6 (CH), 135.6 (CH), 132.6, (q), 132.5 (q), 132.4 (q), 132.4 (q), 130.4 (CH), 130.3 (CH), 130.3 (CH), 129.7 (CH), 129.2 (CH), 128.2 (CH), 128.1 (CH), 124.6 (CH), 110.9 (CH_2), 98.1 (q) , 96.7 (q), 68.2 (q), 63.2 (q), 60.8 (CH_2), 60.8 (CH_2), 40.8 (CH_2), 38.2 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 26.9 (CH_3), 19.3 (q), 13.4 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3068, 2359, 2253, 1785, 1709, 1628, 1428, 1106; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{34}NO_4Si$ $[M+NH_4]^+$ 476.2252, found 476.2247.

8-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-11-methyl-2-oxatricyclo[3.3.3.$0^{1,5}$]undeca-7,10-diene-3,6- dione **283** and

8-{[(tert-butyldiphenylsilyl)oxy]methyl}-11- methylidene-2-oxatricyclo[3.3.3.$0^{1,5}$]undec-7- ene-3,6-dione **284**

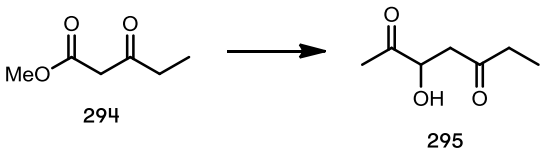


An inseparable mixture *endo*-**283**:*exo*-**284** (1:1.2) (30 mg, 0.065 mmol, 1 equiv) and *p*-TsOH (12.5 mg, 0.065 mmol, 1 equiv) in anhydrous benzene (5 mL) was stirred and heated to reflux for 60 hr. The reaction mixture was diluted with brine and the organic layer separated. The remaining aqueous faction was extcted twice with EtOAc and the organic extracts combined, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished an inseparable mixture of regioisomers *endo*-**283**:*exo*-**284** (3:1) (7 mg, 23% combined yield) as a yellow solid.

Endo*-283/*Exo*-284*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 4H, Ar**H**), 7.52 – 7.34 (m, 6H, Ar**H**), 6.38 (t, *J* = 1.9 Hz, 1H, *exo* CH_2C=C**H**), 6.33 (t, *J* = 1.8 Hz, 1H, *endo* CH_2C=C**H**), 5.30 – 5.21 (m, 2H, *endo* C**H**=CCH_3, *exo* CH_2=C), 5.13 (t, *J* = 1.6 Hz, 1H, *exo* CH_2=C), 4.80 – 4.65 (m, 2H, *endo* CH_2O, *exo* CH_2O), 4.66 – 4.46 (m, 2H, CH_2O, *exo* CH_2O), 2.95 – 2.46 (m, 8H, *endo* CH_2CO, *exo* CH_2CO, 2 × *endo* CH_2, 2 × *exo* CH_2), 2.36 – 2.22 (m, 1H, *exo* CH_2), 2.02 – 1.90 (m, 1H, *exo* CH_2), 1.83 (d, *J* = 1.7 Hz, 3H, *endo* CH_3C=CH), 1.13 – 1.05 (m, 9H, *endo/exo* $SiC(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.1 (q), 201.8 (q), 175.5 (q), 175.0 (q), 174.6 (q), 174.3 (q), 147.5 (q), 137.3 (q), 135.6 (CH), 135.6 (CH), 132.5 (q), 132.4 (q), 132.4 (q), 130.4 (CH), 130.3 (CH), 130.3 (CH), 129.7 (CH), 129.2 (CH), 128.2 (CH), 128.1 (CH), 124.6 (CH), 110.9 (CH), 98.1 (q), 96.7 (q), 68.2 (q), 63.2 (q), 60.8 (CH_2), 60.8

(CH_2), 40.8 (CH_2), 38.2 (CH_2), 34.2 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 26.9 (CH_3), 19.3 (q), 13.4 (CH_3).

3-Hydroxyheptane-2,5-dione **295**

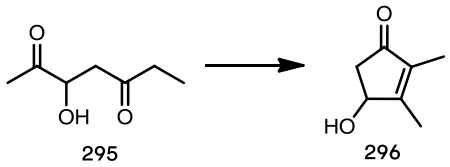


Methyl propionylacetate **294** (20 g, 0.15 mol, 1 equiv) was cooled to 0 °C before being dissolved in a chilled solution of KOH (9.8 g, 0.18 mol, 1.1 equiv) in distilled H_2O (63 mL) and left stirring for 30 mins. The reaction mixture was then placed in the refrigerator for 6 days before CO_2 was bubbled into the solution at RT for 2 hr followed by the addition of pyruvaldehyde (28.5 mL, 40% aqueous solution, 0.13 mol, 0.9 equiv) and left stirring at RT for 24 hr. After which time, the reaction was placed back in the refrigerator for 17 hr and then diluted with EtOAc. The organic layer was separated and the aqueous fraction was extracted an additional three times with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude was purified by vacuum distillation (6 mbar, 128 °C), furnishing 3-hydroxyheptane-2,5-dione **295** as clear and colourless oil (12.9 g, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 – 4.30 (m, 1H, C**H**), 3.72 (d, J = 5.4 Hz, 1H, O**H**), 2.94 (dd, $J_{AB, AX}$ = 17.0, 3.8 Hz, 1H, CHC**H**$_2$CO), 2.82 (dd, $J_{BA, BX}$ = 17.0, 6.4 Hz, 1H, CHC**H**$_2$CO), 2.49 (q, J = 7.2 Hz, 2H, C**H**$_2$CH$_3$), 2.26 (s, 3H, C**H**$_3$CO), 1.06 (t, J = 7.3 Hz,3H, C**H**$_3$CH$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.0 (q), 209.4 (q), 74.0 (CH), 45.0 (CH_2), 37.1 (CH_2), 25.5 (CH_3), 7.5 (CH_3).

The spectroscopic data were in agreement with those previously published.[137]

4-Hydroxy-2,3-dimethylcyclopent-2-enone **296**



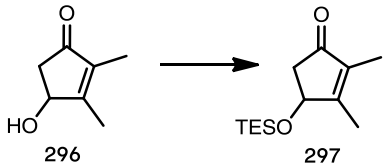
295 296

A solution of diketone **295** (15 g, 0.10 mmol, 1 equiv) in MeOH (75 mL) was cooled to 0 °C. An aqueous solution of 20% K_2CO_3 (470 mL) was added slowly over 1 hr such that the internal temperature of the reaction did not exceed 8 °C. The reaction mixture was stirred for 2 hr at 0 °C before being allowed to warm to RT and left for a further 24 hr. The solution was extracted three times with EtOAc, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 2:8) delivered enone **296** as a clear orange oil (9.49 g, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (t, J = 6.0 Hz, 1H, C**H**), 2.77 (dd, $J_{AB, AX}$ = 18.4, 6.2 Hz, 1H, C**H**$_2$), 2.27 (dd, $J_{BA, BX}$ = 18.4, 1.9 Hz, 1H, C**H**$_2$), 2.23 (d, J = 6.8 Hz, 1H, O**H**), 2.08 (s, 3H, CCC**H**$_3$), 1.71 (s, 3H, CHCC**H**$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.8 (q), 168.3 (q), 138.3 (q), 71.8 (CH), 44.4 (CH_2), 13.8 (CH_3), 8.1 (CH_3).

The spectroscopic data were in agreement with those previously published.[137]

2,3-Dimethyl-4-(triethylsilyloxy)cyclopent-2-enone **297**



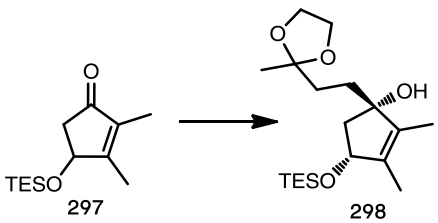
296 297

A solution of enone **296** (13.9 g, 0.11 mol, 1 equiv), triethylamine (18.7 g, 0.12 mol, 1.1 equiv), DMAP (35.4 mL, 0.25 mol, 2.3 equiv) in anhydrous DCM (180 mL) was cooled to 0 °C before slow addition of TESCl (20.4 mL, 0.12 mol, 1.1 equiv). The reaction was stirred for 13 hr at RT before adding brine and separating the organic

layer. The DCM extracts were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) delivered enone **297** as a clear orange oil (23.5 g, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 – 4.63 (m, 1H, C**H**), 2.70 (dd, $J_{AB,\ AX}$ = 18.0, 6.0 Hz, 1H, C**H**$_2$CO), 2.23 (dd, $J_{BA,\ BX}$ = 18.0, 2.0 Hz, 1H, C**H**$_2$CO), 2.01 (s, 3H, CHC=CC**H**$_3$), 1.69 (s, 3H, CHCC**H**$_3$), 0.98 (t, J = 8.0 Hz, 9H, Si(CH_2C**H**$_3$)$_3$), 0.65 (q, J = 7.9 Hz, 6H, Si(C**H**$_2$$CH_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.6 (q), 169.0 (q), 137.7 (q), 71.8 (CH), 45.1 (CH_2), 13.9 (CH_3), 8.1 (CH_3), 6.9 (CH_3), 4.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2956, 1711, 1663, 1064, 1015; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{25}O_2Si$ $[M+H]^+$ 241.1618, found 241.1618.

2,3-Dimethyl-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-4-(triethylsilyloxy)cyclopent-2-enol **298**

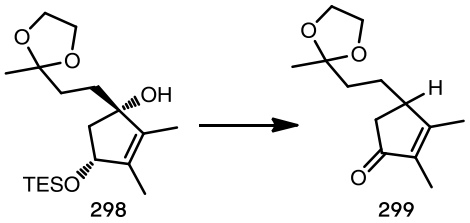


A solution of dioxolane **147** (12.9 g, 53.2 mmol, 1.6 equiv) in anhydrous Et_2O (80 mL) was cooled to –78 °C and stirred for 10 mins before the slow addition of ^{t}BuLi (65.8 mL, 1.7 M solution in pentane, 111.9 mmol, 3.4 equiv). The reaction was stirred for a further 1 hr at –78 °C before being allowed to warm to RT for another 1 hr. After which time, the mixture was cannulated into a precooled solution of enone **297** (8g, 33.3 mmol, 1 equiv) in Et_2O (250 mL) at –78 °C ensuring the internal temperature of the reaction did not exceed –70 °C. The reaction was left stirring for a further 90 mins at –78 °C before warming to RT and quenching with distilled H_2O (10 mL). The solution was dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 6:4)

afforded a single diastereomer of tertiary alcohol **298** as a clear colourless oil (10.23 g, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 – 4.30 (m, 1H, C**H**), 4.00 – 3.85 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.40 (dd, $J_{AB, AX}$ = 13.9, 6.9 Hz, 1H, C**H$_2$**CH), 1.83 – 1.37 (m, 11H, 2 × C**H$_3$**CC, **2** × C**H$_2$**, C**H$_2$**CH), 1.31 (s, 3H, C**H$_3$**CCH$_2$), 0.97 (t, J = 8.0 Hz, 9H, Si(CH$_2$C**H$_3$**)$_3$), 0.65 – 0.58 (m, 6H, Si(C**H$_2$**CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.4 (q), 136.8 (q), 109.9 (q), 83.9 (q), 76.4 (CH), 64.7 (CH_2), 48.1 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 23.9 (CH_3), 11.6 (CH_3), 9.0 (CH_3), 6.8 (CH_3), 4.8 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3444, 2956, 1645, 1458, 1378, 1065; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{36}O_4SiNa$ $[M+Na]^+$ 379.2275, found 379.2276.

2,3-Dimethyl-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone **299**



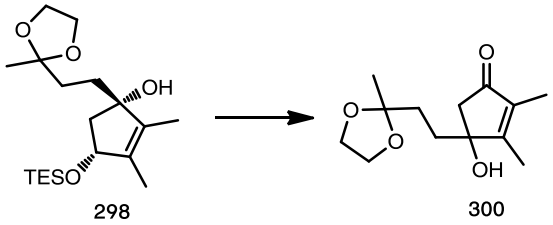
Tertiary alcohol **298** (650 mg, 1.82 mmol, 1 equiv) and TCNQ (37 mg, 0.18 mmol, 0.1 equiv) were dissolved in a solvent mixture of THF:H_2O (10 mL, 9:1) and stirred at RT for 24 hr. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 1:9) afforded enone **299** as a yellow oil (208 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 – 3.84 (m, 4H, OC**H$_2$**C**H$_2$**O), 2.67 (s, 1H, C**H**), 2.49 (dd, $J_{AB, AX}$ = 18.6, 6.5 Hz, 1H, C**H$_2$**CO), 2.04 (dd, $J_{BA, BX}$ = 18.6, 1.9 Hz, 1H, C**H$_2$**CO), 2.00 (s, 3H, CHC=CC**H$_3$**), 1.93 – 1.84 (m, 1H, C**H$_2$**), 1.70 – 1.64 (m, 4H, CHCC**H$_3$**,), 1.61 – 1.55 (m, 2H, C**H$_2$**), 1.36 – 1.26 (m, 4H, C**H$_3$**CCH$_2$, C**H$_2$**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.8 (q), 172.6 (q), 136.9 (q), 109.8 (q), 64.9 (CH_2), 64.8 (CH_2), 42.5 (CH), 40.4 (CH_2), 36.4 (CH_2), 27.0 (CH_2), 24.0 (CH_3), 15.3 (CH_3), 8.1

(CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2950, 2359, 2342, 1698, 1646, 1385, 1061; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{21}O_3$ $[M+H]^+$ 225.1485, found 225.1484.

4-Hydroxy-2,3-dimethyl-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone

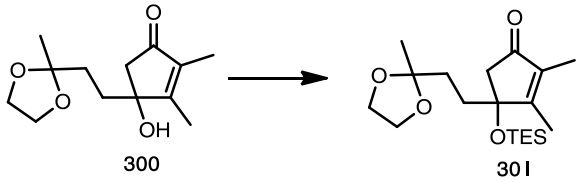
300



A solution of tertiary alcohol **298** (10.2 g, 0.03 mol, 1 equiv) in anhydrous DCM (170 mL was treated with TBAF (40.1 mL, 0.04 mol, 1.4 equiv) and stirred for 1 hr at RT. The reaction mixture was then supplemented with TPAP (0.50 g, 14.3 mmol, 0.05 equiv), NMO (10.1 g, 0.09 mol, 3 equiv) and stirred for a further 20 hr before the reaction solvent was removed under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 100% EtOAc), which afforded cyclopentenone **300** as a brown oil (6.43 g, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 – 3.90 (m, 4H, OCH_2CH_2O), 2.70 – 2.65 (m, 1H, OH), 2.57 (d, *J* = 18.3 Hz, 1H, CCH_2CO), 2.41 (d, *J* = 18.3 Hz, 1H, CCH_2CO), 2.03 – 1.93 (m, 4H, $HOCC=CCH_3$, CH_2), 1.78 – 1.67 (m, 4H, $HOCCCH_3$, CH_2), 1.67 – 1.57 (m, 2H, $CH_3CCH_2CH_2$), 1.33 (s, 3H, CH_3CCH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.5 (q), 170.4 (q), 137.3 (q), 109.7 (q), 78.5 (q), 64.9 (CH_2), 64.9 (CH_2), 48.5 (CH_2), 34.1 (CH_2), 32.3 (CH_2), 24.0 (CH_3), 11.3 (CH_3), 8.1 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3432, 2928, 2359, 1699, 1652, 1381, 1065; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{20}NaO_4$ $[M+Na]^+$ 263.1254, found 263.1257.

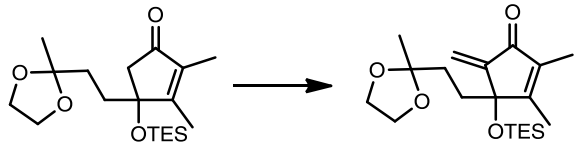
2,3-Dimethyl-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-4-(triethylsilyloxy)cyclopent-2-enone **301**



Cyclopentenone **300** (3 g, 12.5 mmol, 1 equiv) and 2,6-lutidine (6.1 mL, 52.4 mmol, 4.2 equiv) in dry DMF (35 mL) was stirred for 5 mins at RT before the dropwise addition of TESOTf (5.7 mL, 25.0 mmol, 2 equiv). The reaction mixture was stirred for 3 hr before being quenched with distilled H_2O (10 mL) and extracted with Et_2O. The ethereal extracts were washed twice with distilled H_2O to remove any residual DMF, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished the title compound **301** as a pale yellow oil (4.0 g, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 – 3.84 (m, 4H, OCH_2CH_2O), 2.52 (d, J = 18.2 Hz, 1H, CCH_2CO), 2.44 (d, J = 18.2 Hz, 1H, CCH_2CO), 1.97 – 1.86 (m, 4H, $SiOCC{=}CCH_3$, CH_2), 1.68 (s, 3H, $SiOCCCH_3$), 1.63 (td, J = 12.7, 4.0 Hz, 1H, CH_2), 1.53 (td, J = 13.0, 4.0 Hz, 1H, CH_2), 1.37 – 1.25 (m, 4H, CH_3CCH_2, CH_2), 0.90 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.57 – 0.47 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.5 (q), 171.8 (q), 136.7 (q), 109.7 (q), 80.4 (q), 64.8 (CH_2), 64.8 (CH_2), 48.2 (CH_2), 34.2 (CH_2), 34.1 (CH_2), 24.1 (CH_3), 11.6 (CH_3), 8.0 (CH_3), 7.1 (CH_3), 6.4 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2956, 2359, 1709, 1657, 1379, 1071; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{34}NaO_4Si$ $[M+Na]^+$ 377.2119, found 377.2115.

2,3-Dimethyl-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-methylene-4-(triethylsilyloxy)cyclopent-2-enone **302**



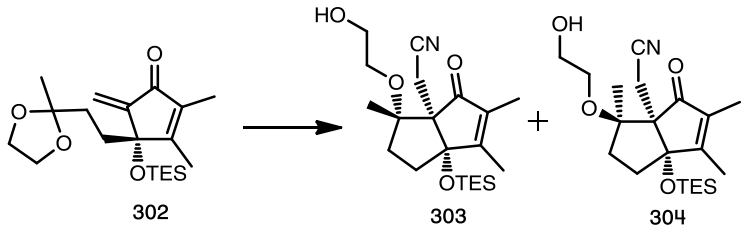
301 **302**

A solution of dioxolane enone **301** (6 g, 16.9 mmol, 1 equiv) in anhydrous THF (60 mL) was cooled –78 °C and stirred for 10 mins before the addition of LDA (28.2 mL, 1.8 M THF/heptane/ethylbenzene, 50.8 mmol, 3 equiv). The reaction was stirred at –78 °C for 1 hr before being allowed to warm to RT and then transferred to a stirred suspension of Eschenmoser's salt (9.4 g, 50.8 mmol, 3 equiv) in dry THF (150 mL) at –78 °C. The resulting solution was left stirring at –78 °C for 2 hr before being allowed to warm to RT and stirred for a further 30 mins. The reaction was quenched with a saturated $NaHCO_3$ solution and extracted with DCM. The DCM extracts were washed with brine, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. The crude orange residue was dissolved in a mixture of DCM:$NaHCO_3$ (120 mL, 2:1) and under vigorous stirring, one portion of *m*CPBA (8.8 g, 50.8 mmol, 3 equiv) was carefully added and left to stir for 30 mins before separating the organic layer. The aqueous layer was extracted with DCM and the combined organic fractions were dried over $MgSO_4$, filtered and solvent removed under reduced pressure leaving an orange crude oil. Flash column chromatography (SiO_2, hexane/EtOAc 2:8) afforded *exo*-methylene **302** as a clear pale yellow oil (4.04 g, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (s, 1H, CH_2=C), 5.50 (s, 1H, CH_2=C), 3.97 – 3.79 (m, 4H, OCH_2CH_2O), 2.04 – 1.94 (m, 4H, $SiOCC=CCH_3$, CH_2), 1.87 (td, J = 13.0, 4.3 Hz, 1H, CH_2), 1.78 (d, J = 0.8 Hz, 3H, $SiOCCCH_3$), 1.31 (td, J = 13.2, 4.3 Hz, 1H, CH_2), 1.25 (s, 3H, CH_3CCH_2), 1.12 (td, J = 13.3, 4.3 Hz, 1H, CH_2), 0.85 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.50 – 0.35 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz,

$CDCl_3$) δ 194.5 (q), 167.1 (q), 147.4 (q), 139.1 (q), 116.0 (CH_2), 109.7 (q), 79.8 (q), 64.8 (CH_2), 64.7 (CH_2), 33.6 (CH_2), 33.2 (CH_2), 23.9 (CH_3), 11.1 (CH_3), 8.3 (CH_3), 7.0 (CH_3), 6.1 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2955, 1706, 1666, 1239, 1378, 1072; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{34}NaO_4Si$ $[M+Na]^+$ 389.2119, found 389.2126.

2-[6a-(Triethylsilyloxy)-3-(2-hydroxyethoxy)-3,5,6-trimethyl-4-oxo-1,2,3,3a,4,6a-hexahydropentalen-3a-yl]acetonitrile **303** and **304**



302 303 304

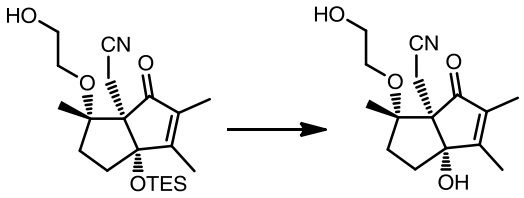
A solution of α-methylene **302** (2 g, 5.5 mmol, 1 equiv) in anhydrous toluene (50 mL) under N_2, cooled to 0 °C and left to stir for 10 mins before dropwise addition of diethylaluminium cyanide (6 mL, 1 M solution in toluene, 6.0 mmol, 1.1 equiv). The reaction mixture was left stirring for 30 mins until the dropwise addition of $TiCl_4$ (6.0 mL, 1M solution in DCM, 6.0 mmmol, 1.1 equiv) and the resultant mixture was left stirring for a further 30 mins before quenching with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 9:11) furnished a separable 7:1 diastereomeric mixture of major diastereomer **303** (1.32 g, 62% yield) as an oil and minor diastereomer **304** (181 mg, 8% yield) as an oil.

Major diastereomer 303: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 – 3.64 (m, 2H, C**H$_2$**OH), 3.51 (ddd, *J* = 10.2, 6.6, 3.8 Hz, 1H, C**H$_2$**OC), 3.37 (ddd, *J* = 9.6, 4.8, 3.6 Hz, 1H, C**H$_2$**OC), 2.60 (d, *J* = 16.5 Hz, 1H, C**H$_2$**CN), 2.49 (d, *J* = 16.5 Hz, 1H, C**H$_2$**CN), 2.13 – 1.86 (m, 6H, SiOCC=CC**H$_3$**, C**H$_2$**, C**H$_2$**), 1.72 (d, *J* = 0.8 Hz, 3H, SiOCCC**H$_3$**), 1.25

(s, 3H, CH_3CCH_2), 1.03 – 0.88 (m, 10H, $Si(CH_2CH_3)_3$, CH_2), 0.78 – 0.66 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.1 (q), 169.1 (q), 136.7 (q), 119.4 (q), 90.2 (q), 83.5 (q), 63.1 (q), 62.8 (CH_2), 62.2 (CH_2), 33.5 (CH_2), 32.0 (CH_2), 18.8 (CH_3), 17.2 (CH_2), 12.5 (CH_3), 8.3 (CH_3), 7.3 (CH_3), 6.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3493, 2954, 2877, 2359, 1704, 1656, 1458, 1237, 1059; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{39}N_2O_4Si$ $[M+NH_4]^+$ 411.2674, found 411.2664.

Minor diastereomer 304: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 – 3.47 (m, 3H, CH_2OH, CH_2OC,), 3.41 – 3.27 (m, 1H, CH_2OC), 2.60 (d, *J* = 16.2 Hz, 1H, CH_2CN), 2.49 (d, *J* = 16.2 Hz, 1H, CH_2CN), 2.26 (s, 1H, OH), 2.07 – 1.99 (m, 4H, $SiOCC{\equiv}CCH_3$, CH_2), 1.92 – 1.80 (m, 2H, $CH_3CCH_2CH_2$), 1.73 – 1.64 (m, 4H, $SiOCCCH_3$, CH_2), 1.36 (s, 3H, CH_3CCH_2), 1.02 – 0.92 (m, 9H, $Si(CH_2CH_3)_3$), 0.77 – 0.67 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.3 (q), 167.4 (q), 137.1 (q), 118.4 (q), 90.4 (q), 83.9 (q), 63.6 (CH_2), 63.2 (q), 62.0 (CH_2), 35.6 (CH_2), 34.4 (CH_2), 19.1 (CH_3), 18.7 (CH_2), 12.4 (CH_3), 8.2 (CH_3), 7.3 (CH_3), 6.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 3465, 2957, 2251, 1704, 1657, 1456, 1241, 1076; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{39}N_2O_4Si$ $[M+NH_4]^+$ 411.2674, found 411.2675.

2-[6a-Hydroxy-3-(2-hydroxyethoxy)-3,5,6-trimethyl-4-oxo-1,2,3,3a,4,6a-hexahydropentalen-3a-yl]acetonitrile **305**

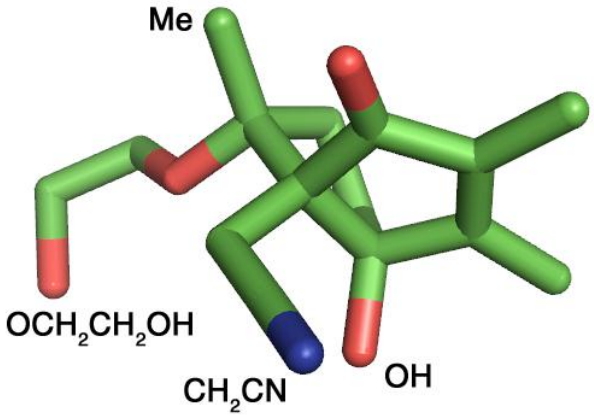


303 305

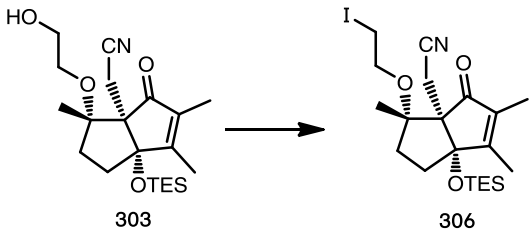
Bicycle **303** (1.4 g, 3.56 mmol, 1 equiv) was dissolved in anhydrous THF (70 mL) and treated with TBAF (4.27 mL, 1 M solution in THF, 4.27 mmol, 1.2 equiv) and stirred for 1 hr at RT. The resulting solution was directly evaporated under reduced pressure leaving a crude mixture that was purified by flash column chromatography (SiO_2, 100% EtOAc) affording diol **305** as a white solid (689 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 – 3.56 (m, 3H, C**H$_2$**OH, O**H**), 3.56 – 3.11 (m, 3H, C**H$_2$**OH, O**H**), 2.80 (d, *J* = 16.8 Hz, 1H, C**H$_2$**CN), 2.56 (d, *J* = 16.8 Hz, 1H, C**H$_2$**CN), 2.09 (s, 3H, SiOCC=CC**H$_3$**), 2.03 – 1.92 (m, 3H, C**H$_2$**, C**H$_2$**), 1.73 (s, 3H, SiOCCC**H$_3$**), 1.28 (s, 3H, C**H$_3$**CCH$_2$), 0.98 – 0.80 (m, 1H, C**H$_2$**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.7 (q), 169.6 (q), 136.7 (q), 120.1 (q), 88.1 (q), 83.9 (q), 62.7 (q), 62.4 (CH_2), 62.2 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 17.6 (CH_3), 16.8 (CH_2), 12.0 (CH_3), 8.2 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3311, 2937, 2873, 2260, 1699, 1657, 1385, 1049; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{25}N_2O_4$ $[M+NH_4]^+$ 297.1809 , found 297.1813; **MP** 133-135 °C.

X-ray crystal structure for **305**:



2-[3-(2-Iodoethoxy)-3,5,6-trimethyl-4-oxo-6a-[(triethylsilyl)oxy]-1,2,3,3a,4,6a-hexahydropentalen-3a-yl]acetonitrile **306**

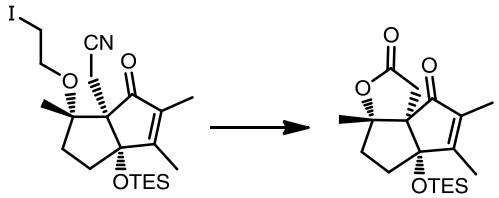


A solution of alcohol **303** (1.2 g, 3.05 mmol, 1 equiv), imidazole (519 mg, 7.62 mmol, 2.5 equiv), PPh_3 (2 g, 7.62 mmol, 2.5 equiv) in dry DCM (60 mL) was stirred at RT. The resulting solution was treated in one portion with I_2 (1548 mg, 6.1 mmol, 2 equiv), stirred for 2 hr before being diluted with saturated $Na_2S_2O_3$ solution and extracted with EtOAc. The EtOAc extracts were washed with brine and dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 9:1) delivered the title compound **306** as a clear yellow oil (1.44 g, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (dt, J = 10.1, 6.9 Hz, 1H, CH_2I), 3.52 (dt, J = 10.2, 6.3 Hz, 1H, CH_2I), 3.26 – 3.16 (m, 2H, CH_2O), 2.68 (d, J = 16.5 Hz, 1H, CH_2CN), 2.57 (d, J = 16.5 Hz, 1H, CH_2CN), 2.09 – 1.98 (m, 4H, SiOCC=CCH_3, CH_2), 1.95 –

1.84 (m, 2H, $CH_3CCH_2CH_2$), 1.72 (d, J = 0.7 Hz, 3H, $SiOCCCH_3$), 1.26 (s, 3H, CH_3CCH_2), 1.03 – 0.97 (m, 9H, $Si(CH_2CH_3)_3$), 0.93 (td, J = 13.7, 6.1 Hz, 1H, CH_2), 0.77 – 0.69 (m, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.0 (q), 169.4 (q), 136.6 (q), 118.6 (q), 90.0 (q), 83.9 (q), 63.3 (q), 62.6 (CH_2), 33.8 (CH_2), 32.4 (CH_2), 18.4 (CH_3), 17.3 (CH_2), 12.5 (CH_3), 8.3 (CH_3), 7.3 (CH_3), 7.0 (CH_2), 3.6 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2954, 2876, 2251, 1704, 1656, 1457, 1237, 1071; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{38}IN_2O_3Si$ $[M+NH_4]^+$ 521.1691, found 521.1690.

5,9,10-Trimethyl-8-[(triethylsilyl)oxy]-4- oxatricyclo[6.3.0.0^{1,5}]undec-9-ene-3, 11-dione **307**



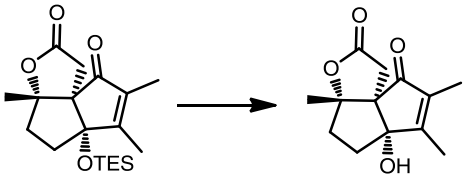
306 307

A solution of bicycle **306** (600 mg, 1.19 mmol, 1 equiv) and activated Zn dust[100] (779 mg, 11.92 mmol, 10 equiv) were dissolved in a solvent mixture of THF:0.1 M AcOH (60 mL, 79:1) and heated to reflux for 19 hr. The resultant suspension was dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished tricycle **307** as a white solid (362 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10 (d, J = 18.3 Hz, 1H, CCH_2CO), 2.72 (d, J = 18.3 Hz, 1H, CCH_2CO), 2.15 (dd, J = 13.0, 6.3 Hz, 1H, CH_2), 2.08 (dd, J = 14.2, 6.7 Hz, 1H, CH_2), 2.03 (s, 3H, $SiOCC{=}CCH_3$), 1.96 (td, J = 13.3, 6.7 Hz, 1H, CH_2, 1.74 (s, 3H, $SiOCCCH_3$), 1.30 (td, J = 13.9, 6.3 Hz, 1H, CH_2), 1.21 (s, 3H, CH_3CCH_2), 0.92 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.62 (q, J = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.2 (q), 175.4 (q), 167.7 (q), 138.3 (q), 93.1 (q), 89.9 (q), 64.8 (q), 34.5 (CH_2), 32.6 (CH_2), 32.3 (CH_2), 23.0 (CH_3), 12.4 (CH_3), 8.6 (CH_3), 7.2 (CH_3),

6.7 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2958, 2877, 1775, 1709, 1652, 1456, 1255, 1136; **HRMS** (ESI) *m/z* calcd for $C_{19}H_{34}NO_4Si$ $[M+NH_4]^+$ 368.2252, found 368.2253; **MP** 52-54 °C.

8-hydroxy-5,9,10-trimethyl-4- oxatricyclo[6.3.0.$0^{1,5}$]undec-9-ene-3,11-dione **308**

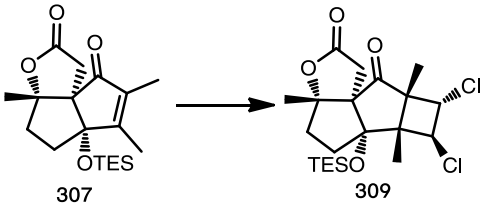


307 308

Tricycle **307** (200 mg, 0.57 mmol, 1 equiv) was dissolved in dry THF (8 mL) and was treated with TBAF (0.86 mL, 1 M solution in THF, 0.86 mmol, 1.5 equiv). The resulting solution was stirred at RT for 1 hr before the solvent was removed. The brown crude oil was purified by flash column chromatography (SiO_2, hexane/EtOAc 4:6) furnishing tertiary alcohol **308** as an off-white solid (130 mg, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08 (d, *J* = 18.2 Hz, 1H, CC**H**$_2$CO), 3.04 (s. br, 1H, O**H**) 2.78 (d, *J* = 18.2 Hz, 1H, CC**H**$_2$CO), 2.22 (dd, *J* = 13.3, 6.5 Hz, 1H, C**H**$_2$), 2.14 – 2.05 (m, 4H, HOCC=CC**H**$_3$, C**H**$_2$), 2.04 – 1.95 (m, 1H, C**H**$_2$), 1.74 (d, *J* = 0.9 Hz, 3H, HOCCC**H**$_3$), 1.40 – 1.30 (m, 1H, C**H**$_2$), 1.25 (s, 3H, C**H**$_3$CCH$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.0 (q), 175.9 (q), 168.0 (q), 138.6 (q), 94.5 (q), 87.9 (q), 63.4 (q), 34.3 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 22.7 (CH_3), 11.8 (CH_3), 8.6 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3430, 2980, 2253, 1765, 1707, 1648, 1387, 1210, 907; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{20}NO_4$ $[M+NH_4]^+$ 254.1387, found 254.1381; **MP** 122-124 °C.

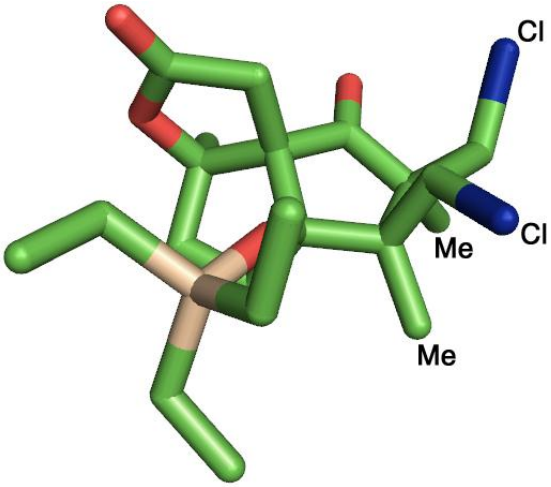
10,11-Dichloro-5,9,12-trimethyl-8-[(triethylsilyl)oxy]-4-oxatetracyclo[6.5.0.0^{1,5}.0^{9,12}]tridecane- 3,13-dione **309**



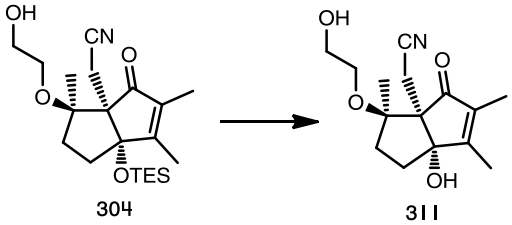
Tricycle **307** (250 mg, 0.71 mmol, 1 equiv) was dissolved in neat *trans*-1,2-dichloroethylene (12 mL) under Argon and in a quartz tube, and was irradiated with a Rayonet photochemical reactor equipped with 254 nm tubes (6 × 10W) for 4 hr at RT. The reaction mixture was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (SiO_2, hexane/EtOAc 3:1) affording as a single diastereomer, tetracycle **309** as a white solid (141 mg, 44% yield). A small single crystal was formed on slow evaporation from a solution of tetracycle **309** in a solvent mixture of hexane and DCM that was suitable for X-ray crystallography.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (d, *J* = 8.9 Hz, 1H, C**H**Cl), 4.01 (d, *J* = 8.9 Hz, 1H, C**H**Cl), 2.99 (d, *J* = 2.2 Hz, 2H, CC**H$_2$**CO), 2.23 (dt, *J* = 13.6, 6.7 Hz, 1H, C**H$_2$**), 2.16 – 2.08 (m, 1H, C**H$_2$**), 1.99 (dt, *J* = 13.7, 6.7 Hz, 1H, C**H$_2$**), 1.72 – 1.63 (m, 1H, C**H$_2$**), 1.30 (s, 3H, C**H$_3$**CCH$_2$), 1.27 (s, 3H, C**H$_3$**CCH), 1.18 (s, 3H, C**H$_3$**CCH), 0.99 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C**H$_3$**)$_3$), 0.75 – 0.67 (m, 6H, Si(C**H$_2$**CH$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.2 (q), 173.9 (q), 95.2 (q), 90.2 (q), 70.3 (q), 63.9 (CH), 62.1 (CH), 57.6 (q), 55.0 (q), 37.3 (CH_2), 35.3 (CH_2), 34.9 (CH_2), 23.4 (CH_3), 16.5 (CH_3), 12.2 (CH_3), 7.3 (CH_3), 6.9 (CH_2); **IR** (thin film, NaCl plate, cm^{-1}) 2957, 1767, 1740, 1454, 1204, 1072, 1241, 1204, 1076; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{36}Cl_2NO_4Si$ $[M+NH_4]^+$ 464.1785, found 464.1785; **MP** 139-141 °C.

X-ray crystal structure for **309**:



2-[6a-Hydroxy-3-(2-hydroxyethoxy)-3,5,6-trimethyl-4-oxo-1,2,3,3a,4,6a-hexahydropentalen-3a-yl]acetonitrile **311**

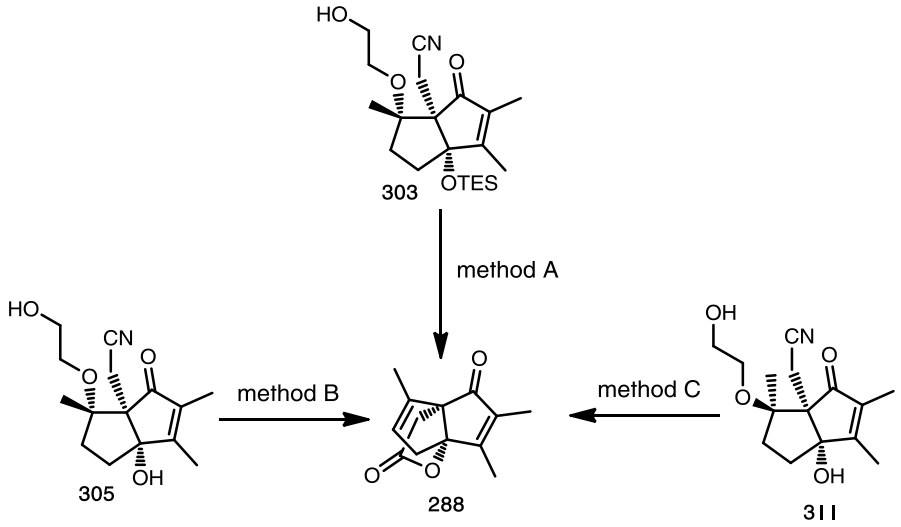


A solution of bicycle **304** (320 mg, 0.81 mmol, 1 equiv) in dry THF (4 mL) was treated with TBAF (0.97 mL, 1 M solution in THF, 0.97 mmol, 1.2 equiv) and stirred at RT for 30 mins. The resulting solution was evaporated under reduced pressure and purified by flash column chromatography (SiO_2, 100% EtOAc) furnishing diol **311** as an amber coloured oil (187 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 – 3.51 (m, 2H, C**H$_2$**O), 3.47 (ddd, J = 9.0, 5.8, 3.2 Hz, 1H, C**H$_2$**OC), 3.31 (ddd, J = 9.1, 6.0, 3.1 Hz, 1H, C**H$_2$**OC), 2.70 – 2.58 (m, 2H, C**H$_2$**CN), 2.37 (s. br, 1H. O**H**), 2.19 (s. br, 1H, O**H**), 2.12 – 2.02 (m, 4H, HOCC=CC**H$_3$**, C**H$_2$**), 2.01 – 1.91 (m, 1H, C**H$_2$**), 1.90 – 1.76 (m, 2H, C**H$_2$**), 1.72 (d, J = 0.9 Hz, 3H, HOCCC**H$_3$**), 1.38 (s, 3H, C**H$_3$**CCH$_2$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 204.1

(q), 167.4 (q), 137.1 (q), 119.0 (q), 88.6 (q), 84.8 (q), 63.3 (CH_2), 62.2 (q), 62.0 (CH_2), 35.1 (CH_2), 34.6 (CH_2), 18.8 (CH_3), 18.3 (CH_2), 11.5 (CH_3), 8.1 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3446, 2956, 2360, 2341, 2251, 1699, 1653, 1385; **HRMS** (ASA) *m/z* calcd for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1543, found 280.1548.

7,8,11-Trimethyl-2- oxatricyclo[3.3.3.$0^{1,5}$]undeca-7,10-diene-3,6-dione **288**



Method A: A solution of alcohol **303** (200 mg, 0.51 mmol, 1 equiv) in anhydrous toluene (13 mL) was treated with $BF_3{\cdot}Et_2O$ (1.3 mL, 10.2 mmol, 20 equiv) and heated to 75 °C for 7 hr before the addition of distilled H_2O (1 mL). The resulting biphasic solution was left for a further 1 hr before diluting with brine. EtOAc extractions were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) furnished lactone **288** as an off-white solid (39.2 mg, 35% yield).

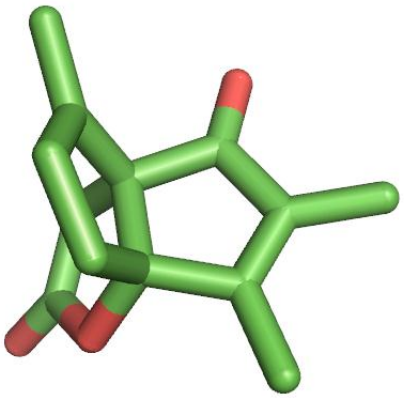
Method B: A solution of diol **305** (240 mg, 0.86 mmol, 1 equiv) in anhydrous toluene (15 mL) was treated with $BF_3{\cdot}Et_2O$ (2.2 mL, 17.2 mmol, 20 equiv) and heated to 100 °C for 3 hr before the addition of distilled H_2O (2.5 mL). The resulting biphasic solution was left for a further 1 hr before diluting with brine. EtOAc extractions were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash

column chromatography (SiO_2, hexane/EtOAc 8:2) delivered lactone **288** as an off-white solid (162 mg, 86% yield).

Method C: A solution of diol **311** (95 mg, 0.34 mmol, 1 equiv) in anhydrous toluene (4 mL) was treated with $BF_3.Et_2O$ (0.85 mL, 6.8 mmol, 20 equiv) and heated to 100 °C for 2 hr before the addition of distilled H_2O (1 mL). The resulting biphasic solution was left for a further 1 hr before diluting with brine. EtOAc extractions were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 8:2) delivered lactone **288** as an off-white solid (61 mg, 82% yield).

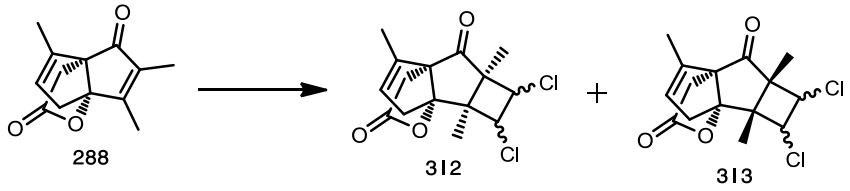
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 – 5.25 (m, 1H, C**H**=C), 2.86 – 2.61 (m, 4H, C**H$_2$**CH=C, CC**H$_2$**CO), 2.12 (d, *J* = 0.9 Hz, 3H, COCC=CC**H$_3$**), 1.87 – 1.79 (m, 3H, C**H$_3$**C=CH), 1.73 (d, *J* = 0.9 Hz, 3H, COCCC**H$_3$**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 203.2 (q), 175.2 (q), 164.0 (q), 138.1 (q), 137.8 (q), 124.2 (CH), 98.3 (q), 66.2 9 (q), 40.4 (CH_2), 34.7 (CH_2), 13.5 (CH_3), 12.6 (CH_3), 8.3 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 1773, 1697, 1643, 1196, 1148, 943; **HRMS** (ESI) *m/z* calcd for $C_{13}H_{18}NO_3$ $[M+NH_4]^+$ 236.1281, found 236.1280; **MP** 132-134 °C.

X-ray crystal structure for **288:**



3,4-Dichloro-2,5,13-trimethyl-10-oxatetracyclo[5.3.3.$0^{1,7}$.$0^{2,5}$]tridec-12-ene- 6,9-dione

312 and **313**



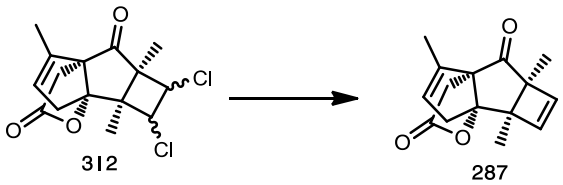
A solution of tricycle **288** (250 mg, 1.14 mmol, 1 equiv) in neat *trans*-1,2-dichloroethylene (20 mL) under Argon and in a quartz tube was irradiated with a Rayonet photochemical reactor equipped with 254 nm tubes (6 × 10W) for 48 hr at RT. The reaction mixture was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (SiO_2, hexane/EtOAc 8:2) affording a separable mixture of photoadducts **312, 313** and unreacted starting material **288** (234 mg). The recovered starting material was recycled furnishing a final separable mixture of diastereomers **312:313** (2:1), **312** as a white solid (148 mg, 41% yield) and **313** as a white solid (70 mg, 19% yield).

Major diastereomer 312: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.55 (d, *J* = 1.6 Hz, 1H, C**H**=C), 4.28 (d, *J* = 8.4 Hz, 1H, C**H**Cl), 3.96 (d, *J* = 8.4 Hz, 1H, C**H**Cl), 2.92 – 2.83 (m, 2H, CC**H$_2$**CO, C**H$_2$**), 2.73 – 2.58 (m, 3H, CC**H$_2$**CO, C**H$_2$**), 1.86 – 1.82 (m, 3H, C**H$_3$**C=CH), 1.38 (s, 3H, C**H$_3$**CCH), 1.20 (s, 3H, C**H$_3$**CCH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 214.4 9 (q), 173.7 (q), 141.7 (q), 127.9 (CH), 99.2 (q), 72.3 (q), 61.9 (CH), 61.2 (CH), 57.9 (q), 54.7 (q), 39.4 (CH_2), 38.8 (CH_2), 17.2 (CH_3), 14.1 (CH_3), 11.0 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2974, 2931, 2866, 2256, 1788, 1739, 1448, 1194, 978, 733; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}Cl_2NO_3$ $[M+NH_4]^+$ 332.0815, found 332.0818.

Minor diastereomer 313: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.44 – 5.37 (m, 1H, C**H**=C), 4.07 (d, *J* = 8.7 Hz, 1H, C**H**Cl), 3.84 (d, *J* = 8.7 Hz, 1H, C**H**Cl), 2.99 – 2.66 (m, 4H, CC**H$_2$**CO, C**H$_2$**), 1.79 – 1.74 (m, 3H, C**H$_3$**C=CH), 1.40 (s, 3H, C**H$_3$**CCH), 1.18 (s, 3H,

CH_3CCH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.9 (q), 173.9 (q), 137.3 (q), 125.7 (CH), 98.8 (q), 70.6 (q), 63.2 (CH), 61.5 (CH), 59.9 (q), 53.7 (q), 40.7 (CH_2), 35.0 (CH_2), 16.7 (CH_3), 13.1 (CH_3), 12.4 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2983, 2360, 1788, 1651, 1450, 1373, 1242, 1034, 858; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}Cl_2NO_3$ $[M+NH_4]^+$ 332.0815, found 332.0820; **MP** 133-135 °C.

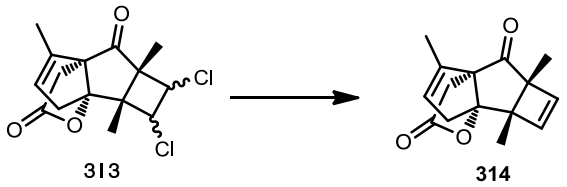
2,5,13-Trimethyl-10- oxatetracyclo[5.3.3.$0^{1,7}$.$0^{2,5}$]trideca-3,12- diene-6,9-dione **287**



Photoadduct **312** (100 mg, 0.32 mmol, 1 equiv), acetic anhydride (747 µL, 7.95 mmol, 25 equiv), activated zinc dust[100] (16.6 g, 154 mmol, 800 equiv) and TMSCl (101 µL, 0.795 mmol, 2.5 equiv) in anhydrous toluene (15 mL). The resulting solution was stirred and heated to 100 °C for 17 hr. After this time, the zinc was removed by filtration and evaporation of the solvent, left a crude residue that was purified by flash column chromatography (SiO_2, hexane/EtOAc 17:3) affording cyclobutene **287** as a yellow solid (57 mg, 73% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, J = 2.8 Hz, 1H, C**H**=CH), 6.08 (d, J = 2.8 Hz, 1H, CH=C**H**), 5.23 – 5.18 (m, 1H, C**H**=C), 2.93 – 2.84 (m, 2H, CC$\mathbf{H_2}$CO, C$\mathbf{H_2}$), 2.66 – 2.59 (m, 1H, C$\mathbf{H_2}$), 2.52 (d, J = 18.6 Hz, 1H, CC$\mathbf{H_2}$CO), 1.73 – 1.68 (m, 3H, C$\mathbf{H_3}$C=CH), 1.37 (s, 3H, C$\mathbf{H_3}$CCH), 1.15 (s, 3H, C$\mathbf{H_3}$CCH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.0 (q), 175.0 (q), 145.2 (CH), 145.0 (q), 140.5 (CH), 124.3 (CH), 97.1 (q), 71.9 (q), 63.3 (q), 57.5 (q), 40.0 (CH_2), 38.9 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 13.4 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2978, 1775, 1721, 1240, 1215, 1069, 963, 766; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}NO_3$ $[M+NH_4]^+$ 262.1438, found 262.1441.

2,5,13-Trimethyl-10- oxatetracyclo[5.3.3.$0^{1,7}$.$0^{2,5}$]trideca-3,12- diene-6,9-dione **314**

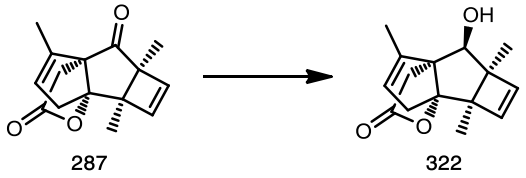


Photoadduct **313** (42 mg, 0.13 mmol, 1 equiv), acetic anhydride (314 µL, 3.3 mmol, 25 equiv), activated zinc dust[100] (7.0 g, 107 mmol, 800 equiv) and TMSCl (42 µL, 0.33 mmol, 2.5 equiv) in anhydrous toluene (6 mL). The resulting solution was stirred and heated to 100 °C for 17 hr. After which time, the zinc was removed by filtration and evaporation of the solvent, left a crude residue that was purified by flash column chromatography (SiO_2, hexane/EtOAc 17:3) affording cyclobutene **314** as yellow solid (24 mg, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, *J* = 2.7 Hz, 1H, C**H**=CH), 6.11 (d, *J* = 2.7 Hz, 1H, C**H**=CH), 5.39 – 5.34 (m, 1H, C**H**=C), 2.82 – 2.76 (m, 3H, CC**H$_2$**CO, C**H$_2$**), 2.70 – 2.63 (m, 1H, C**H$_2$**), 1.84 – 1.80 (m, 3H, C**H$_3$**C=CH), 1.35 (s, 3H, C**H$_3$**CCH), 1.18 (s, 3H, C**H$_3$**CCH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.8 (q), 175.2 (q), 145.4 (CH), 140.7 (CH), 137.4 (q), 125.3 (CH), 98.1 (q), 69.2 (q), 66.4 (q), 56.2 (q), 40.2 (CH_2), 38.8 (CH_2), 16.1 (CH_3), 12.9 (CH_3), 12.7 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 2979, 1771, 1719, 1443, 1234, 1200, 1165, 1030, 941, 770; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{20}NO_3$ $[M+NH_4]^+$ 262.1438, found 262.1442.

6-Hydroxy-2,5,13-trimethyl-10- oxatetracyclo[5.3.3.$0^{1,7}$.$0^{2,5}$]trideca-3,

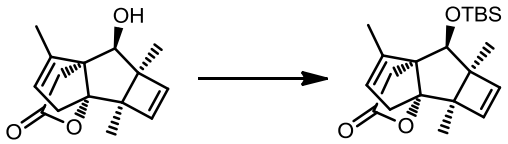
12- dien-9-one **322**



A solution of tetracycle **287** (30 mg, 0.12 mmol, 1 equiv) in anhydrous MeOH (3 mL) was treated in one portion with sodium borohydride (9.3 mg, 0.25 mmol, 2 equiv). The reaction mixture was left stirring for 2 hr before being quenched with 0.5 mL distilled water, dried over $MgSO_4$, filtered and solvent evaporated under reduced pressure. Flash column chromatography (SiO_2, hexane/EtOAc 7:3) furnished **322** as a clear colourless oil (24.4 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 – 6.07 (m, 2H, C**H**=CH, CH=C**H**), 5.25 (d, *J* = 1.6 Hz, 1H, C**H**=C), 3.70 (d, *J* = 7.5 Hz, 1H, C**H**OH), 2.75 (d, *J* = 17.8 Hz, 1H, CC**H$_2$**CO), 2.63 – 2.54 (m, 2H, CC**H$_2$**CO, C**H$_2$**), 2.51 – 2.43 (m, 1H, C**H$_2$**), 1.82 – 1.76 (m, 3H, C**H$_3$**C=CH), 1.50 (d, *J* = 7.7 Hz, 1H, O**H**), 1.18 (s, 3H, C**H$_3$**CCH), 1.17 (s, 3H, C**H$_3$**CCH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.3 (q), 143.0 (q), 141.5 (CH), 138.0 (CH), 125.4 (CH), 100.0 (q), 83.1 (CH), 68.4 (q), 61.9 (q), 58.6 (q), 42.6 (CH_2), 40.5 (CH_2), 19.3 (CH_3), 15.8 (CH_3), 14.6 (CH_3) **IR** (thin film, NaCl plate, cm^{-1}) 3435, 3037, 2925, 1770, 1446, 1379, 945, 768; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{18}O_3$ $[M+H]^+$ 247.1340, found 247.1340.

6-[(*tert*-Butyldimethylsilyl)oxy]-2,5,13-trimethyl-10-oxatetracyclo[5.3.3.$0^{1,7}$.$0^{2,5}$]trideca- 3,12-dien-9-one **320**



322 **320**

Tertiary alcohol **322** (20 mg, 0.08 mmol, 1 equiv) and triethylamine (69 mg, 1.70 mmol, 21 equiv) were dissolved in anhydrous DCM (3 mL) followed by the addition in one portion of TBSOTf (186 µL, 0.81 mmol, 10 equiv). The reaction mixture was carefully heated to 30 °C and left stirring for 5 days until most of the starting material had been consumed. The reaction mixture was diluted with brine, extracted twice with DCM and the organic layers combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexane/EtOAc 1:19) furnished **320** as a clear colourless viscous oil (23.6 mg, 81% yield) and unreacted starting material **322** (2 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, *J* = 2.9 Hz, 1H, C**H**=CH), 5.88 (d, *J* = 2.9 Hz, 1H, CH=C**H**), 5.12 (d, *J* = 1.5 Hz, 1H, C**H**=C), 3.64 (s, 1H, C**H**OSi), 2.77 (d, *J* = 17.6 Hz, 1H, CC**H**$_2$CO), 2.57 – 2.50 (m, 1H, C**H**$_2$), 2.45 (d, *J* = 17.7 Hz, 1H, CC**H**$_2$CO), 2.41 – 2.34 (m, 1H, C**H**$_2$), 1.82 – 1.75 (m, 3H, C**H**$_3$C=CH), 1.16 (s, 3H, OCCC**H**$_3$), 1.08 (s, 3H, SiOCHCC**H**$_3$), 0.91 (s, 9H, SiC(C**H**$_3$)$_3$), 0.12 – 0.09 (m, 6H, Si(C**H**$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.7 (q), 145.6 (q), 139.7 (CH), 138.9 (CH), 124.1 (CH), 100.4 (q), 83.6 (CH), 65.3 (q), 59.7 (q), 57.9 (q), 44.6 (CH_2), 39.8 (CH_2), 26.1 (CH_3), 19.1 (CH_3), 18.2 (q), 17.4 (CH_3), 13.7 (CH_3), -2.9 (CH_3), -4.7 (CH_3); **IR** (thin film, NaCl plate, cm^{-1}) 3039, 2929, 2856, 2360, 2254, 1780, 1732, 1257; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{32}O_3Si$ $[M+H]^+$ 361.2204, found 361.2202

The spectroscopic data were in agreement with those previously published.[22]

7 References

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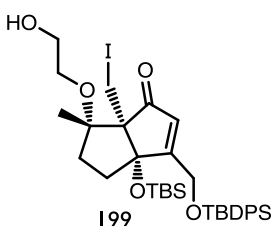
(143) *To a rapidly stirred solution of 2.0 g. of CuI and AcOH (50 mL) was added Zn dust (35 g). The couple was filtered before being washed with AcOH (50 mL) and Et_2O (3 × 100 mL). The wet Zn-Cu was vacuum dried before being ready for use.*

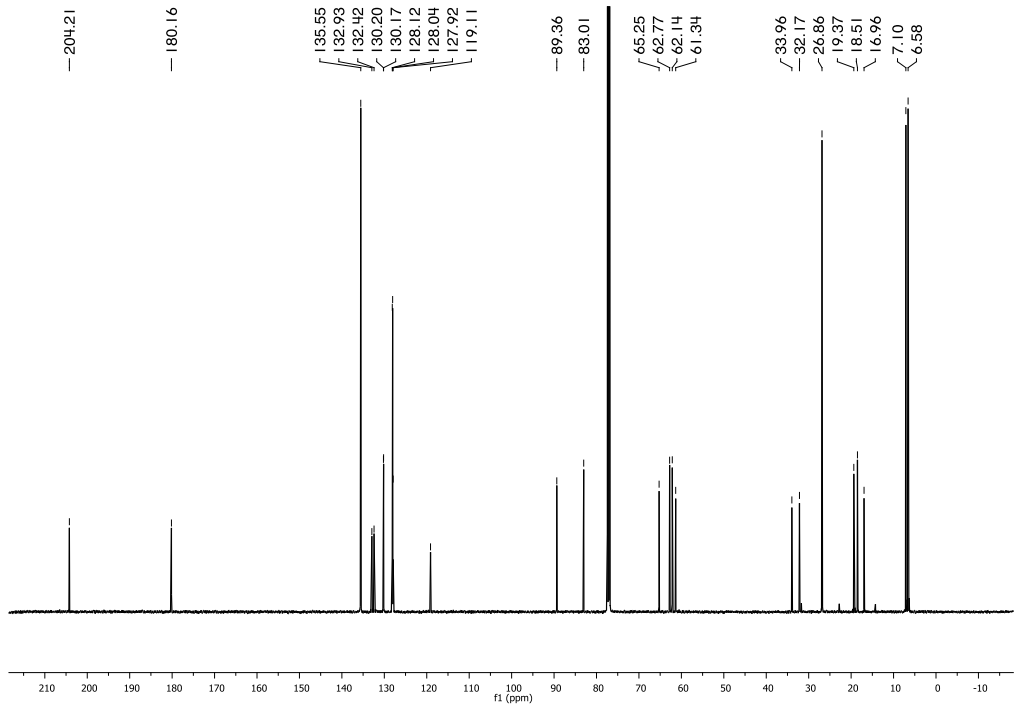
Appendix: Spectroscopic Data

Iodo-aldol product **199**

^{1}H-NMR (600 MHz, $CDCl_3$), ^{13}C-NMR (91 MHz, $CDCl_3$)

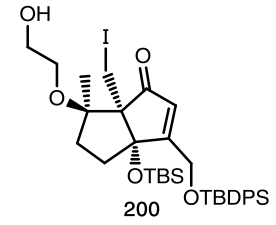


199

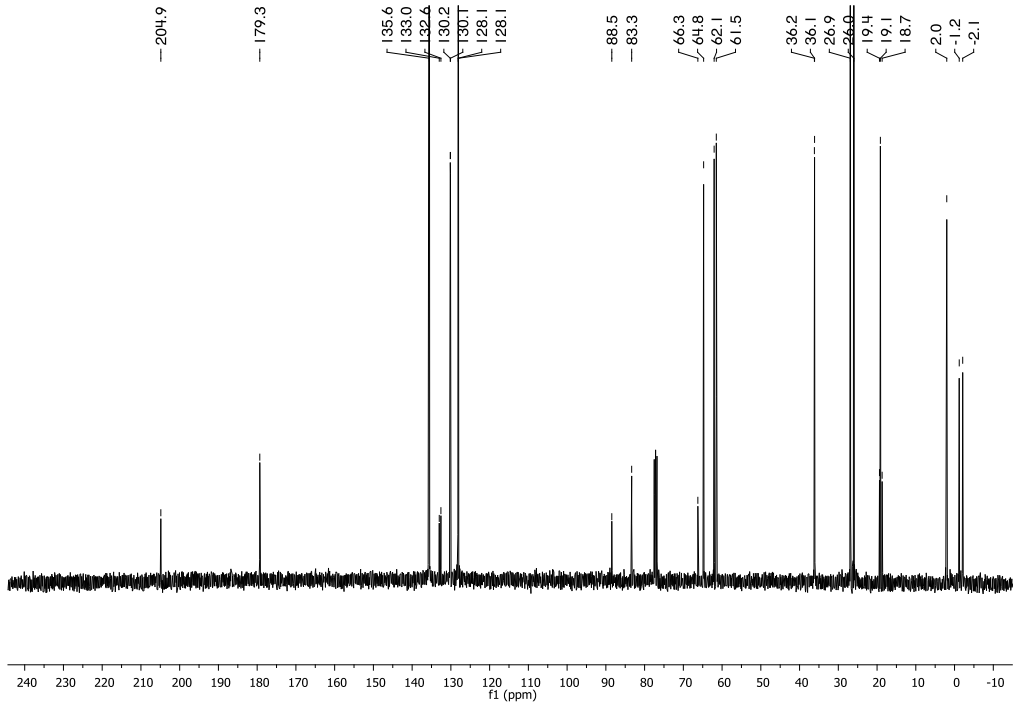


Iodo-aldol product **200**

^{1}H-NMR (600 MHz, $CDCl_3$), ^{13}C-NMR (91 MHz, $CDCl_3$)

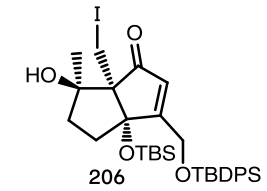


200

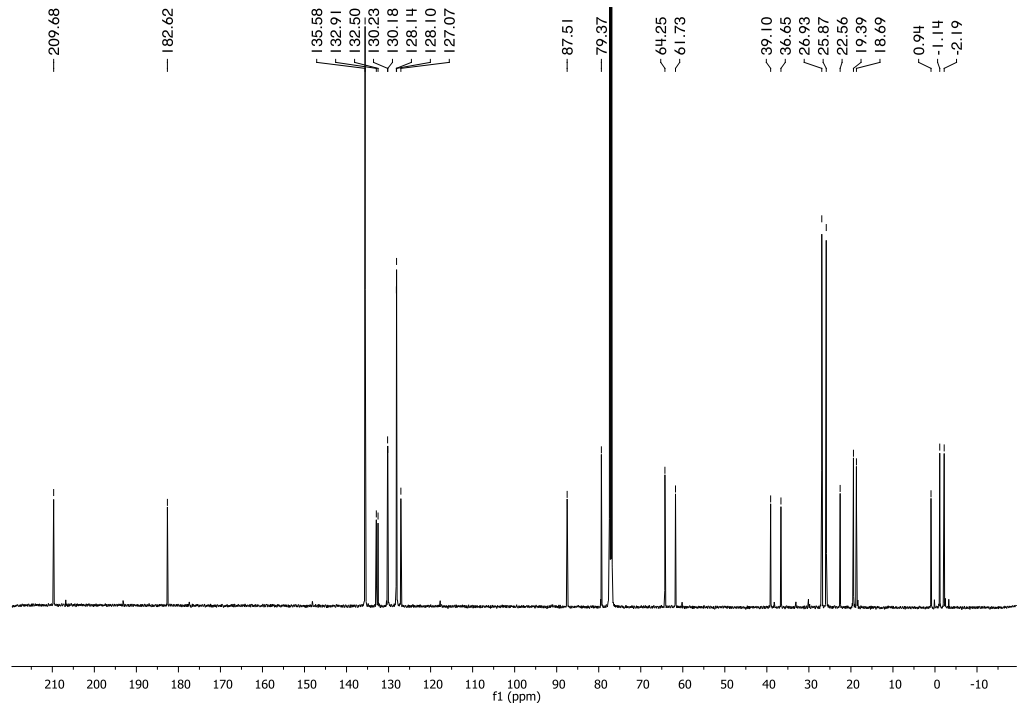


Iodol-aldol product **206**

^{1}H-NMR (600 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

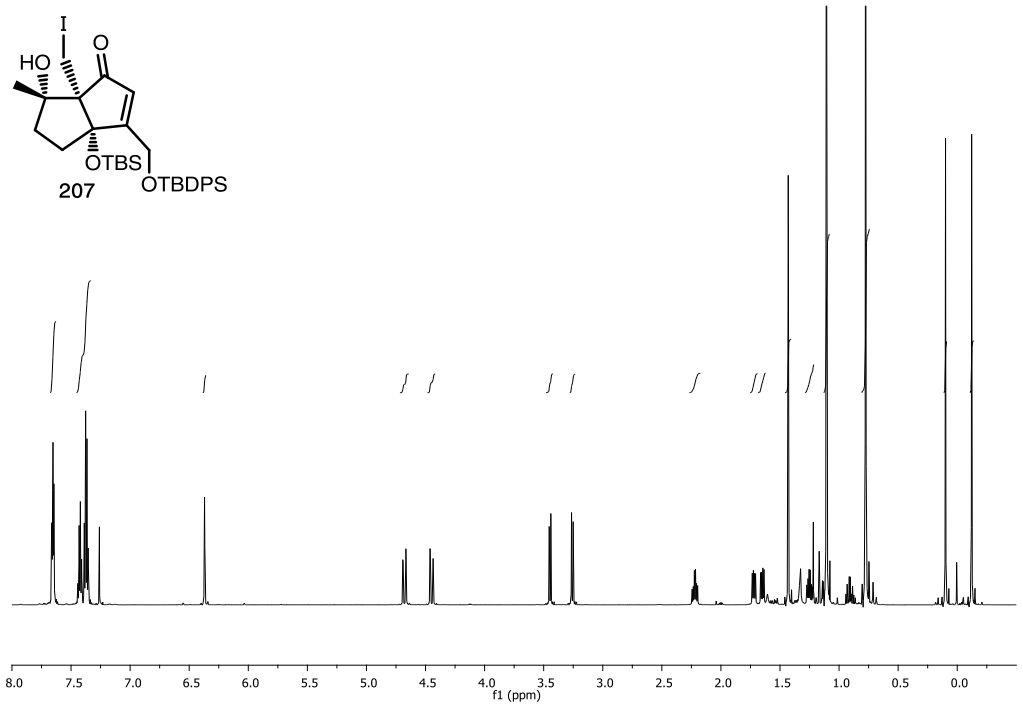


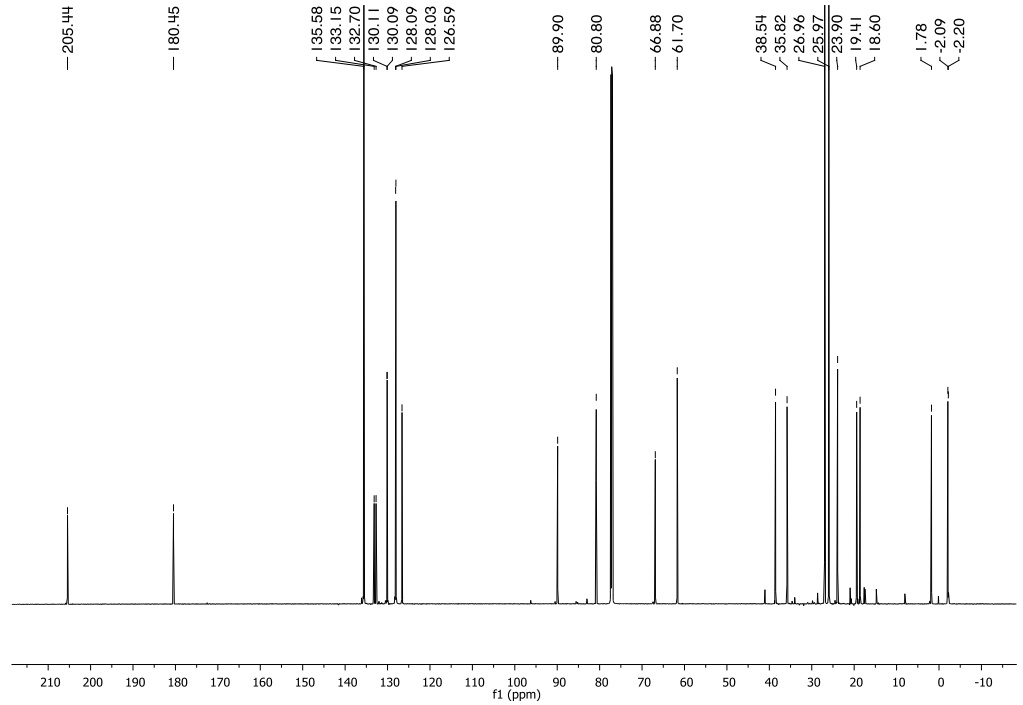
206



Iodol-aldol product **207**

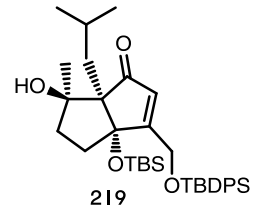
^{1}H-NMR (700 MHz, $CDCl_3$), ^{13}C-NMR (176 MHz, $CDCl_3$)



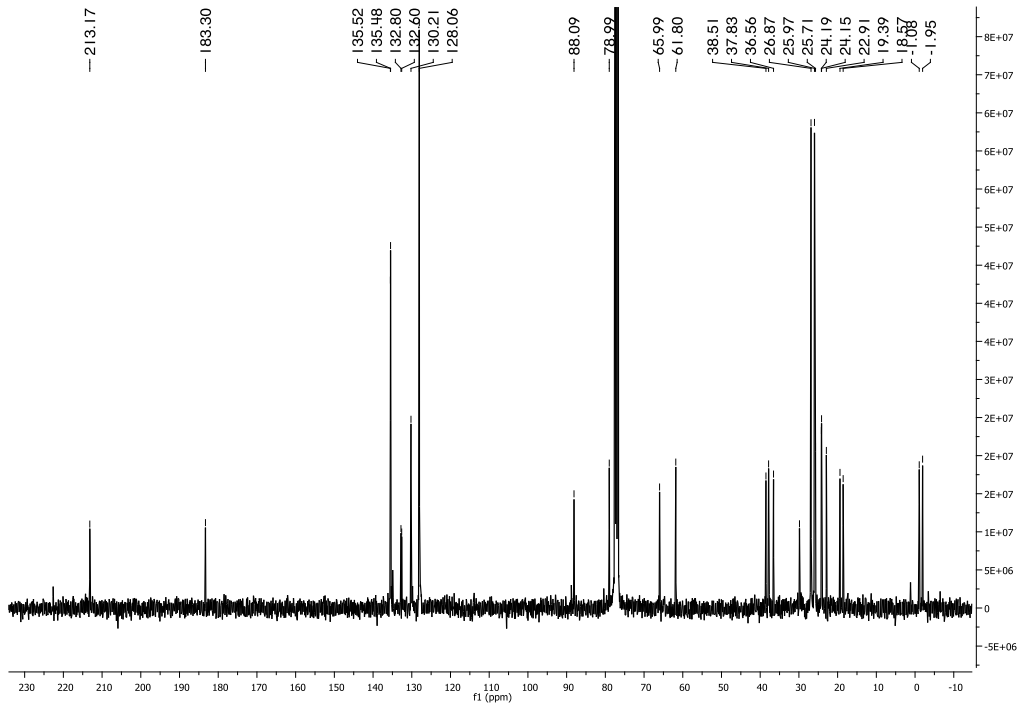


Isopropyl **219**

^{1}H-NMR (600 MHz, $CDCl_3$), ^{13}C-NMR (91 MHz, $CDCl_3$)

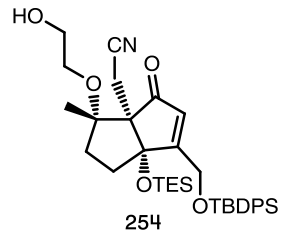


219

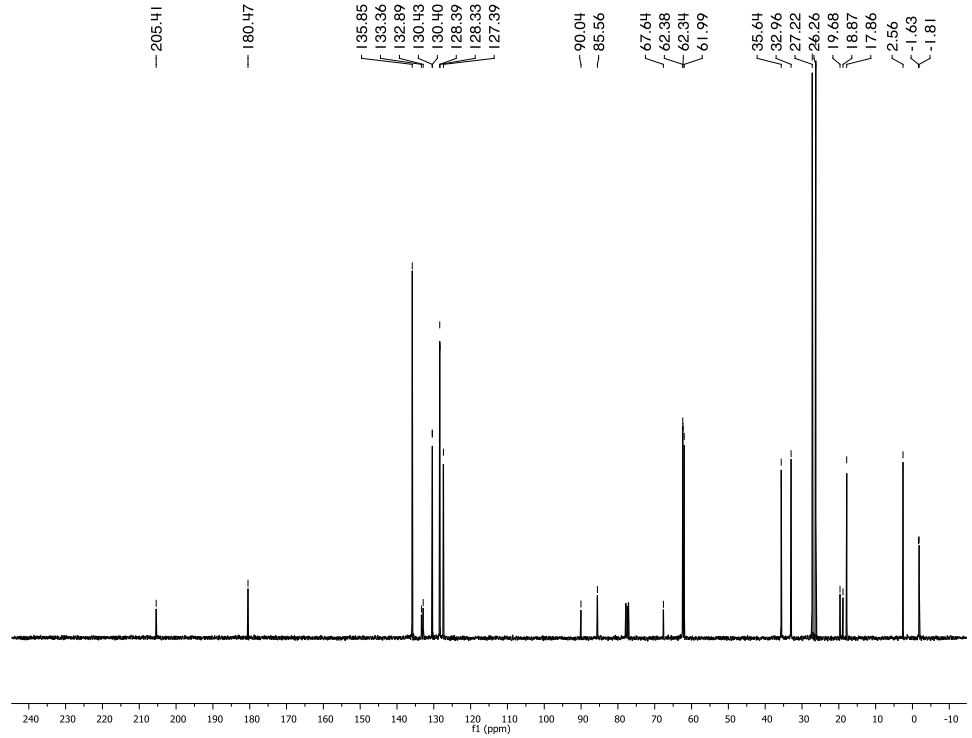


Cyano-aldol product **254**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

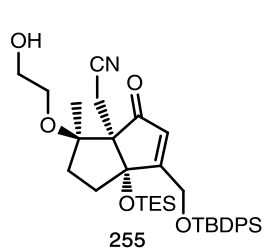


254

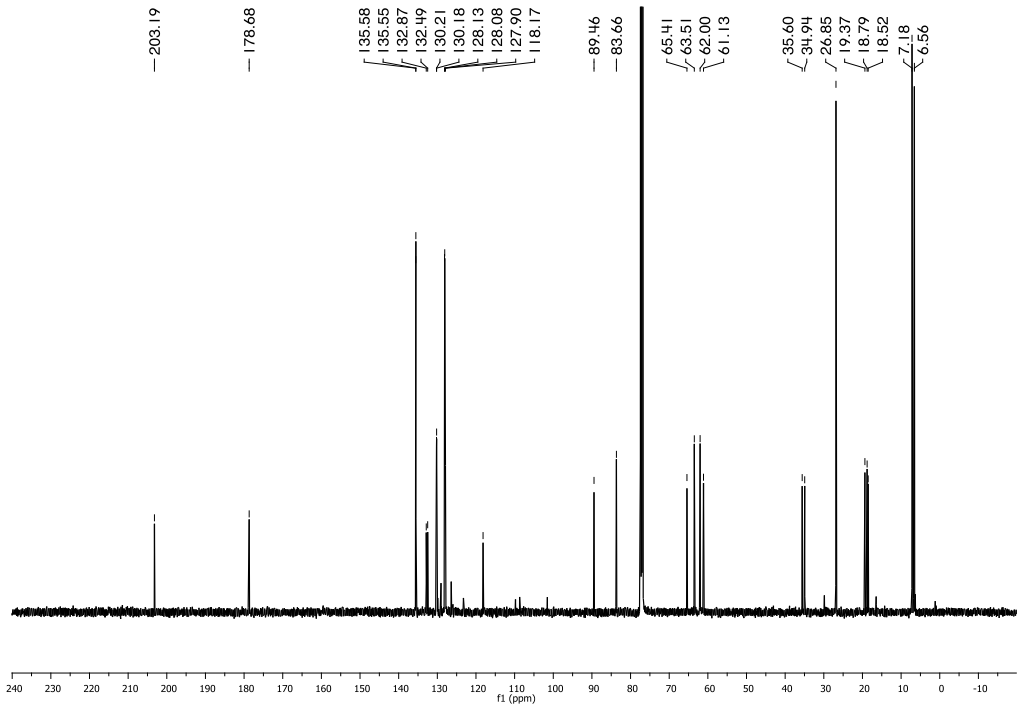


Cyano-aldol product **255**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

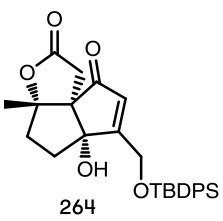


255

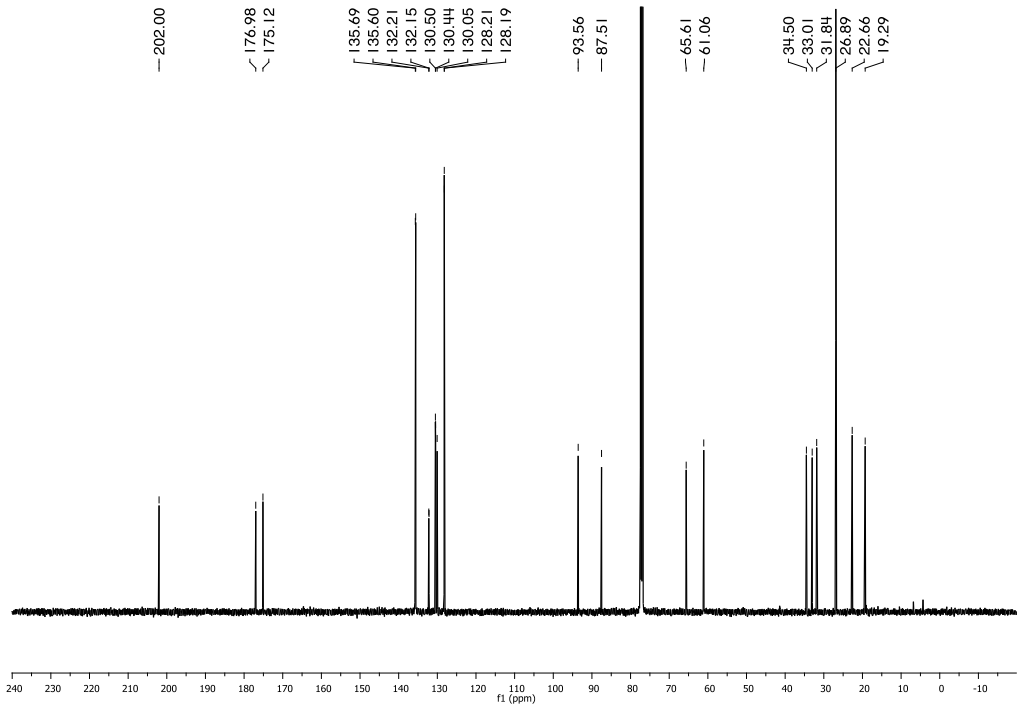


Tricycle product **264**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

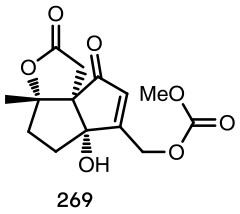


264

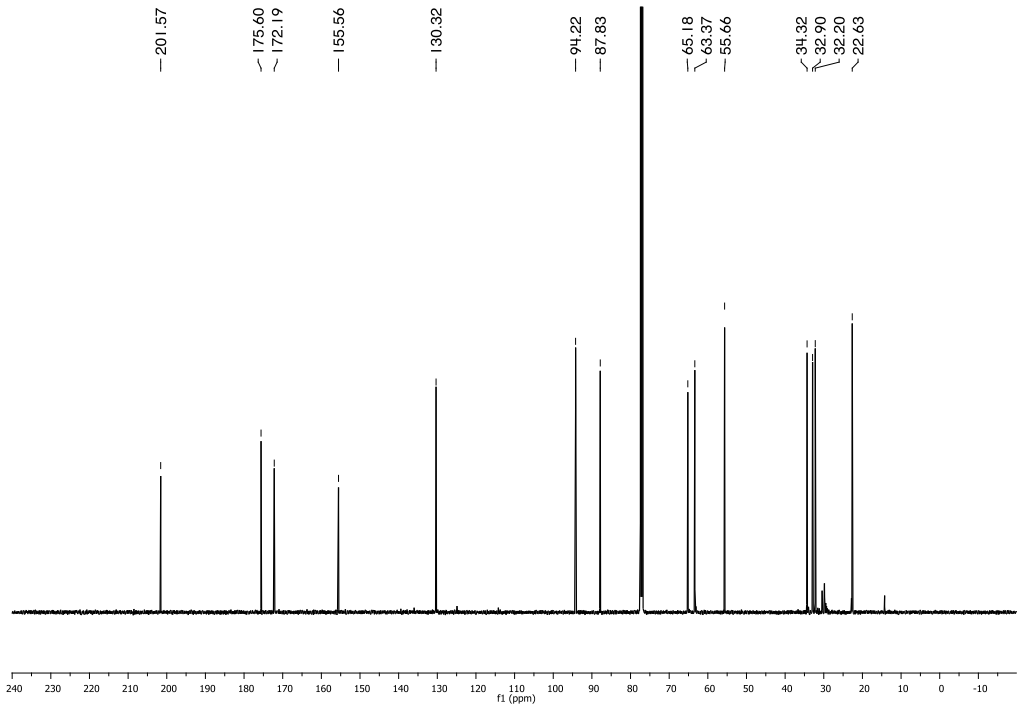


Carbonate **269**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

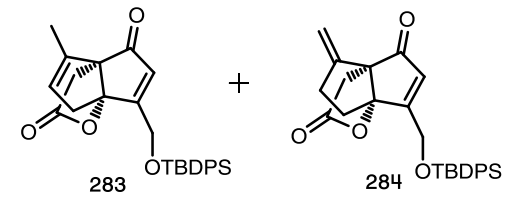


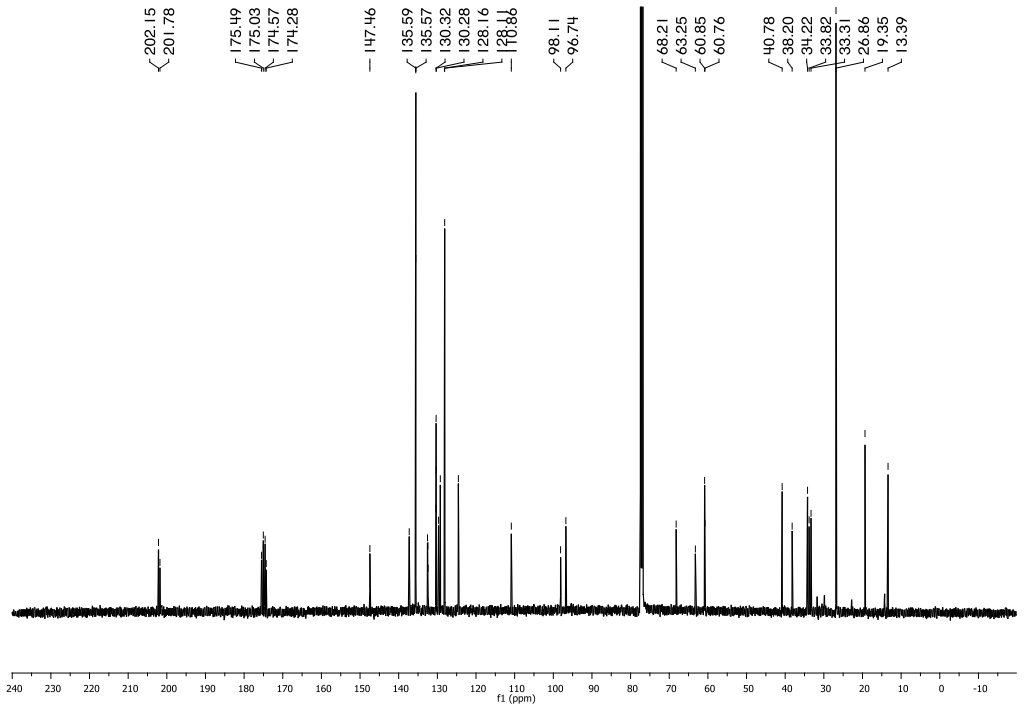
269



Tricycles **283** and **284**

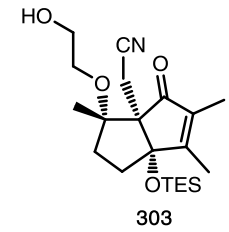
^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)



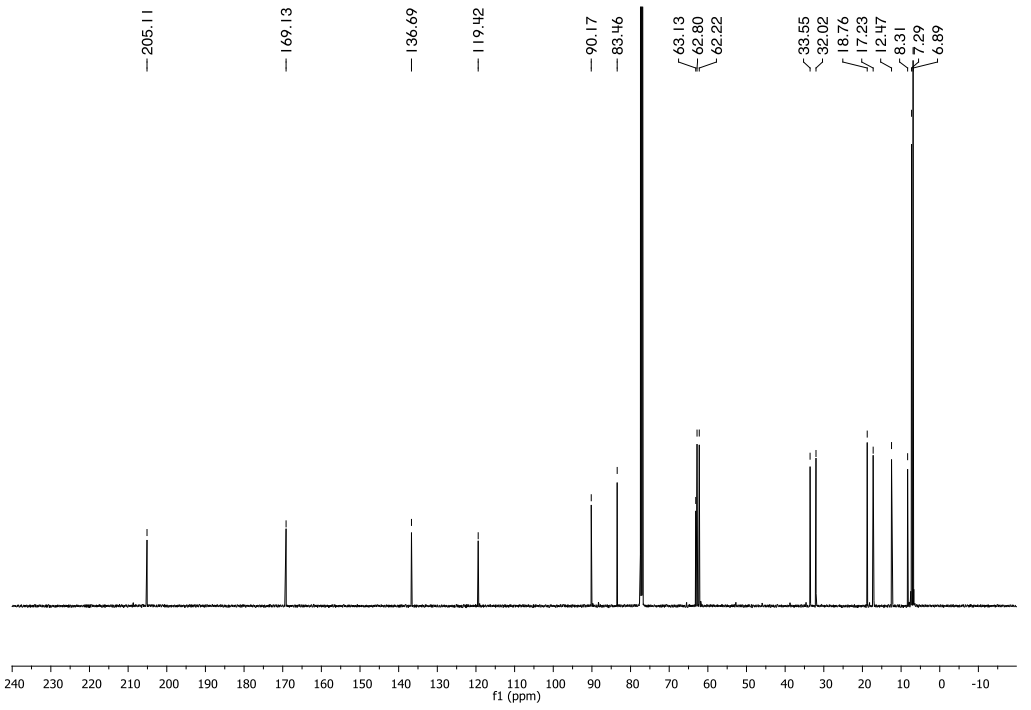


Cyano-aldol product **303**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

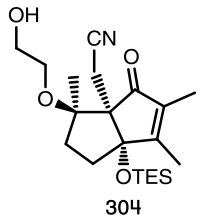


303

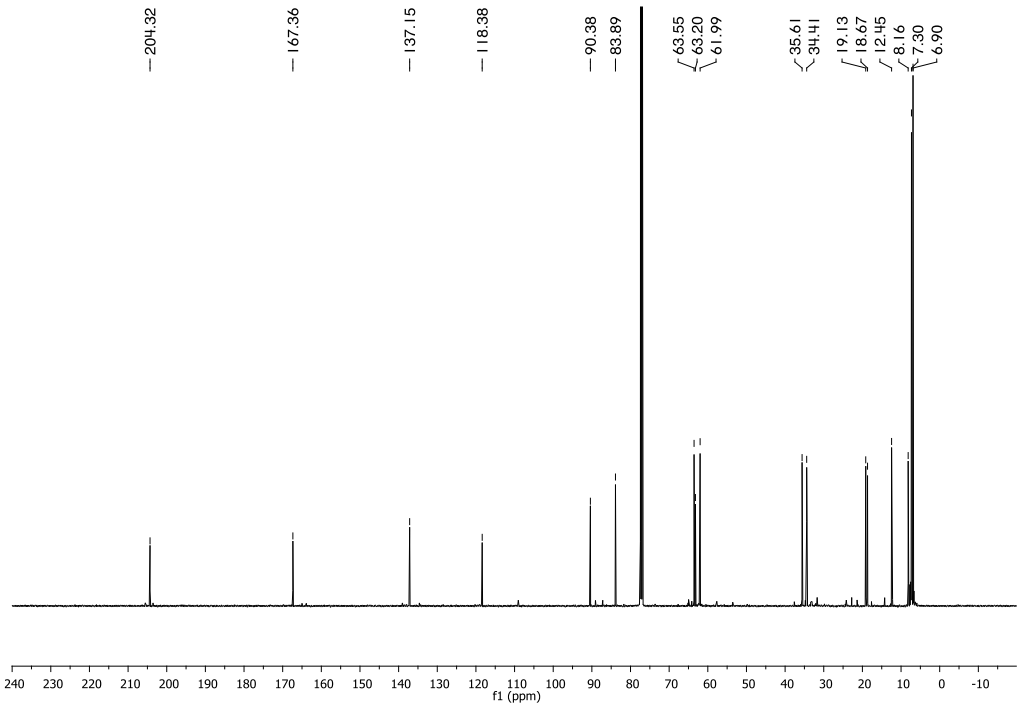


Cyano-aldol product **304**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

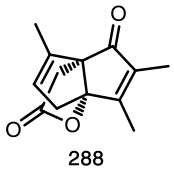


304

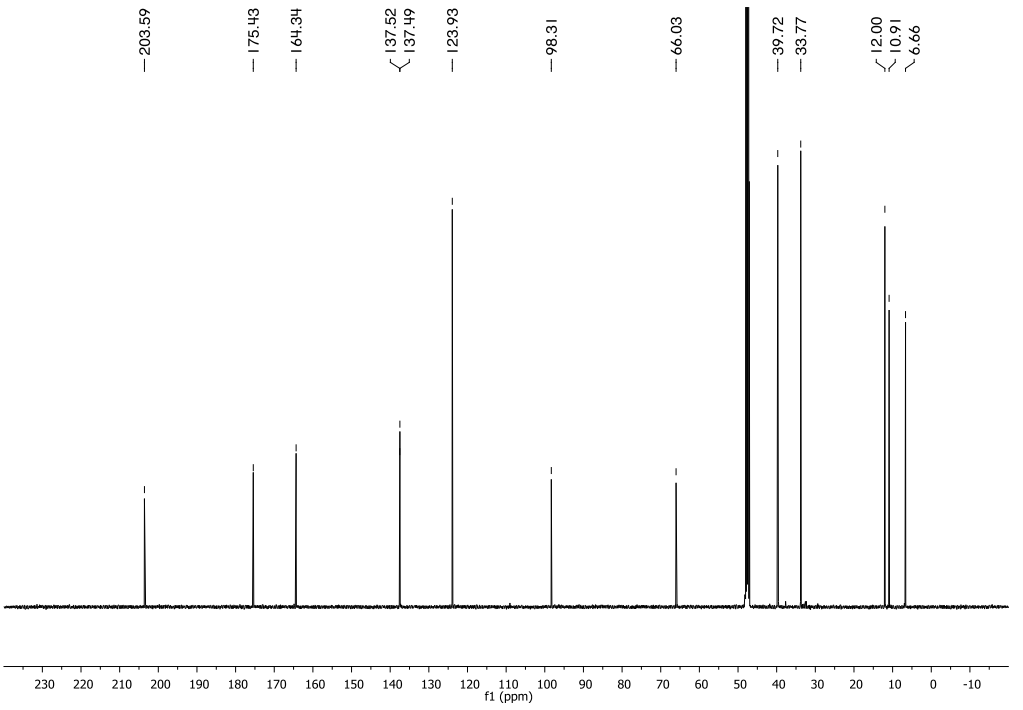


Tricycle **288**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, CD_3OD)

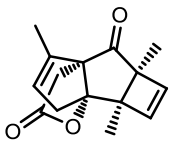


288

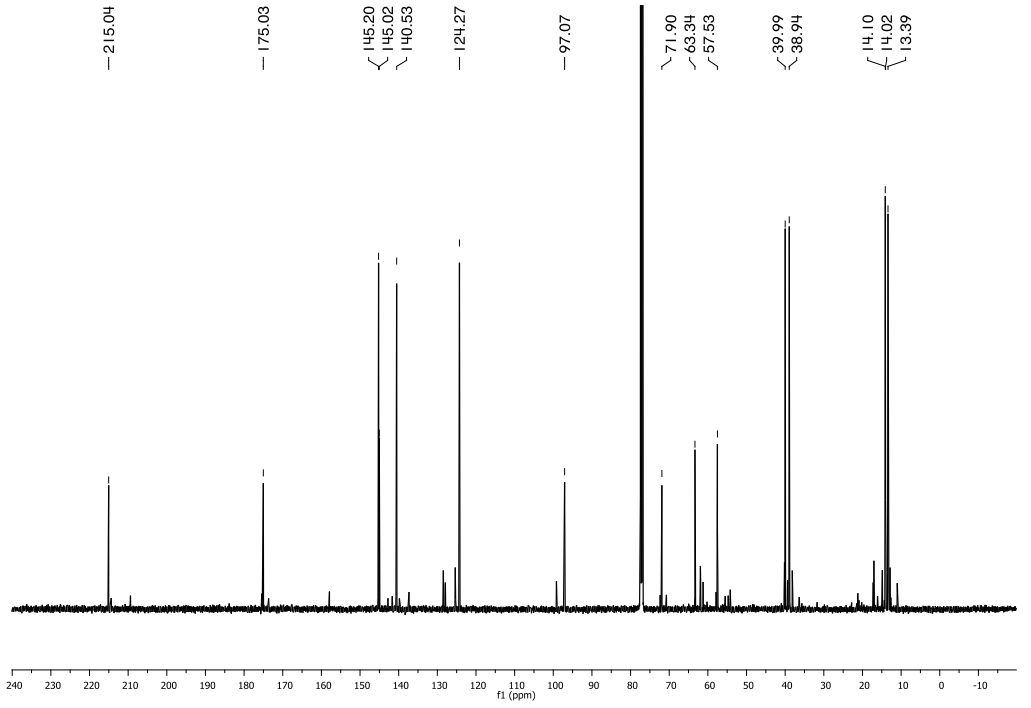


Cyclobutene **287**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

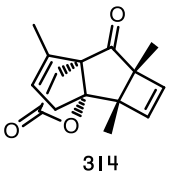


287

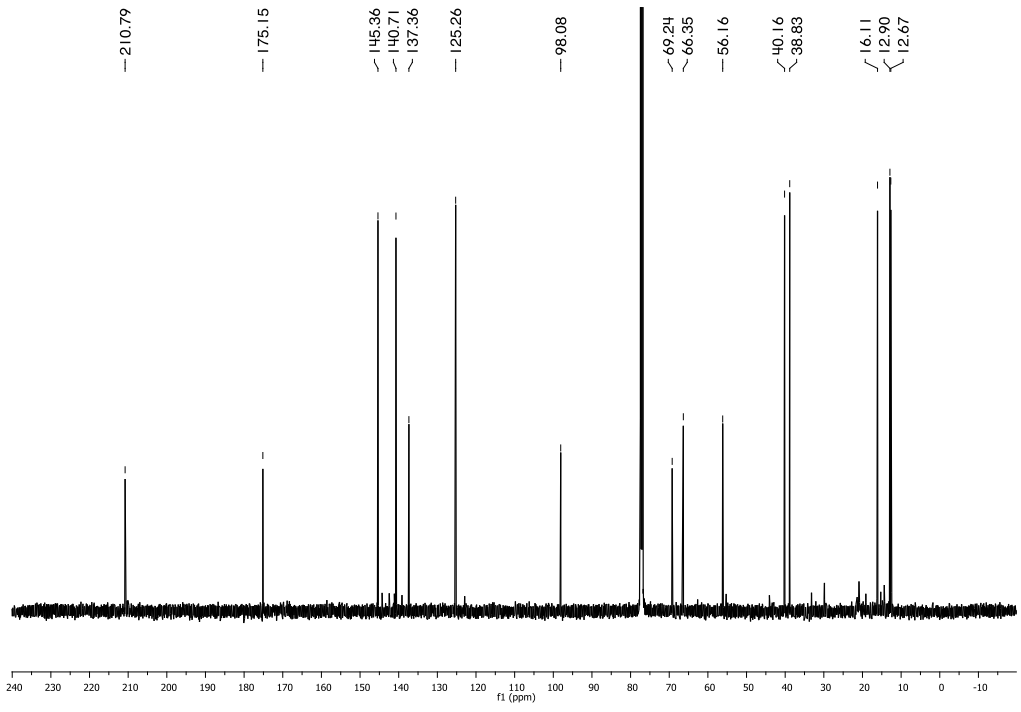


Cyclobutene **314**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

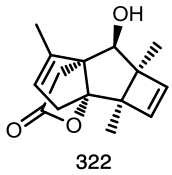


314

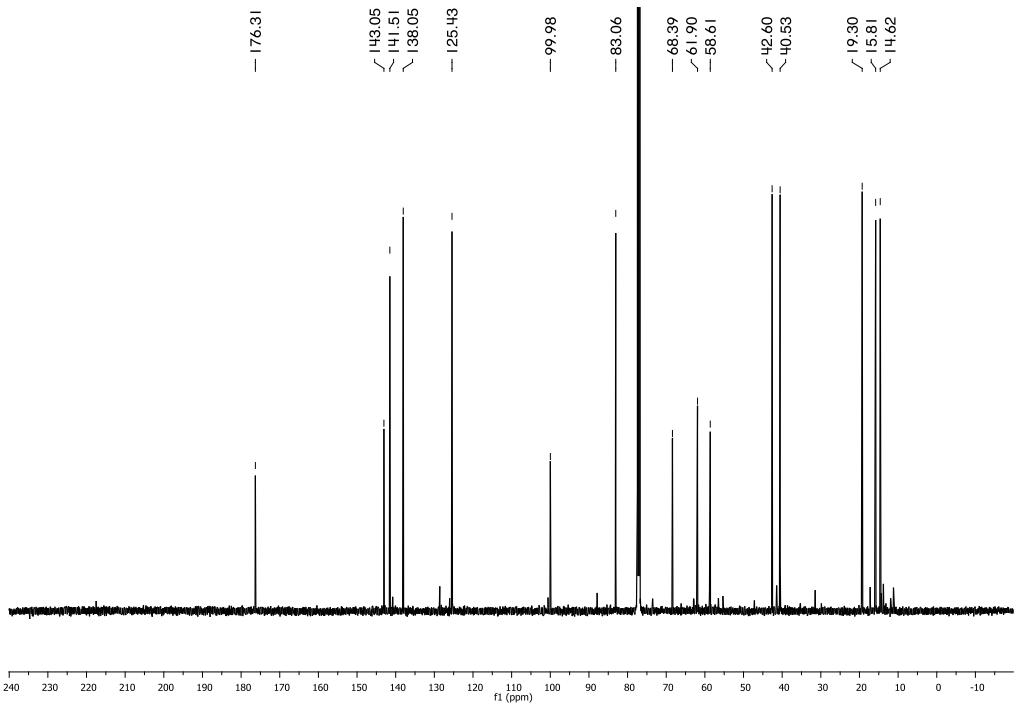


Tetracycle **322**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)

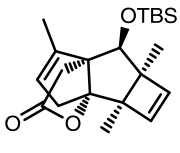


322



Tetracycle **320**

^{1}H-NMR (500 MHz, $CDCl_3$), ^{13}C-NMR (126 MHz, $CDCl_3$)



320